plasticity and reduce amyloid deposition in APP/PS1 mice. Thus, Kv1.3 channel may be a therapeutic target for Alzheimer's disease.

[0013] Kv1.3 channel blockers could be also useful for ameliorating pathology in cardiovascular disorders such as ischemic stroke, where activated microglia significantly contributes to the secondary expansion of the infarct.

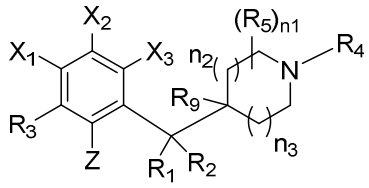
[0014] Kv1.3 channel expression is associated with the control of proliferation in multiple cell types, apoptosis, and cell survival. These processes are crucial for cancer progression. In this context, Kv1.3 channels located in the inner mitochondrial membrane can interact with the apoptosis regulator Bax (Serrano-Albarras, A., *et al*., 2018, *Expert Opin. Ther. Targets*, 101-105). Thus, inhibitors of Kv1.3 channels may be used as anticancer agents.

[0015] A number of peptide toxins with multiple disulfide bonds from spiders, scorpions, and anemones are known to block Kv1.3 channels. A few selective, potent peptide inhibitors of the Kv1.3 channel have been developed. A synthetic derivative of stichodactyla toxin (shk) with an unnatural amino acid (shk-186) is the most advanced peptide toxin. Shk has demonstrated efficacy in preclinical models and is currently in a phase I clinical trial for treatment of psoriasis. Shk can suppress proliferation of TEM cells resulting in improved condition in animal models of multiple sclerosis. Unfortunately, Shk also binds to the closely-related Kvi channel subtype found in CNS and heart. There is a need for Kv1.3 channel-selective inhibitors to avoid potential cardio- and neuro-toxicity. Additionally, small peptides like shk-186 are rapidly cleared from the body after administration, resulting in short circulating half-lives, frequent administration events. Thus, there is a need for the development of long-acting, selective Kv1.3 channel inhibitors for the treatment of chronic inflammatory diseases.

[0016] Thus, there remains a need for development of novel Kv1.3 channel blockers as pharmaceutical agents.

SUMMARY

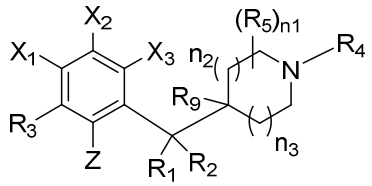
[0017] Compounds useful as potassium channel blockers having a structure of Formula I,



I , are described, where the various substituents are defined herein. The compounds of Formula I described herein can block Kv1.3 potassium (K^+) channels and be used in the treatment of a variety of conditions. Methods for synthesizing these

compounds are also described herein. Pharmaceutical compositions and methods of using these compositions described herein are useful for treating conditions *in vitro* and *in vivo*. Such compounds, pharmaceutical compositions, and methods of treatment have a number of clinical applications, including as pharmaceutically active agents and methods for treating cancer, an immunological disorder, a Central Nerve System (CNS) disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular disorder, a kidney disease or a combination thereof.

[0018] In one example, a compound of Formula I or a pharmaceutically acceptable salt thereof is described,



I ;

where

Z is OR_a, NR_aR_b, or $NR_b(C=O)R_a$;

X_1 is H, halogen, CN, alkyl, halogenated alkyl, cycloalkyl, cycloalkenyl, or halogenated cycloalkyl;

X_2 is H, halogen, CN, alkyl, halogenated alkyl, cycloalkyl, or halogenated cycloalkyl;

X_3 is H, halogen, fluorinated alkyl, or alkyl;

or alternatively X_1 and X_2 and the carbon atoms they are connected to taken together form an optionally substituted 6-membered aryl;

or alternatively X_2 and X_3 and the carbon atoms they are connected to taken together form an optionally substituted 6-membered aryl;

R_3 is H, halogen, or alkyl;

or alternatively X_1 and R_3 and the carbon atoms they are connected to taken together form an optionally substituted 6-membered aryl;

connected to form an optionally substituted heterocycle including the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

each occurrence of R_8 is independently H, alkyl, or an optionally substituted heterocycle; or alternatively the two R_8 groups together with the nitrogen atom that they are connected to form an optionally substituted heterocycle including the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

R_9 is H, alkyl, halogen, or $(CR_6R_7)_{n4}OR_b$;

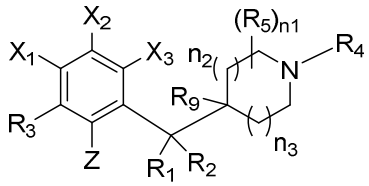
the alkyl, cycloalkyl, spiroalkyl, bicycloalkyl, heterocycle, aryl, and heteroaryl in X_1, X_2, X_3, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_a, R_b, R_c, and R_d, where applicable, are optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, cycloalkyl, halogenated cycloalkyl, halogenated alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)C_{1-4}$alkyl, $(C=O)N(R_8)_2$, and oxo where valence permits;

each occurrence of n_1 is independently an integer from 0-3 where valence permits;

each occurrence of n_2 and n_3 is independently an integer from 0-2; and

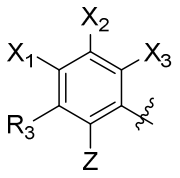
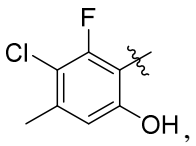
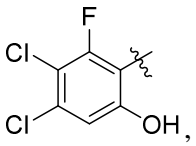
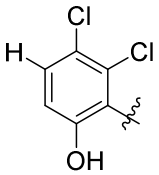
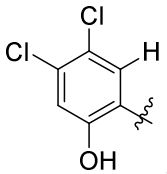
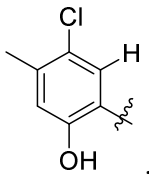
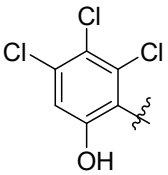
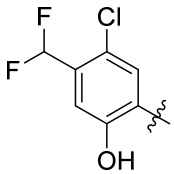
each occurrence of n_4 is independently an integer from 0-3.

[0018a] In an aspect, there is provided a compound of Formula I or a pharmaceutically acceptable salt thereof,



I ;

wherein

the structural moiety  has the structure of , , , , , , or , each of

which is substituted by R_3;

R_3 is H, halogen, or alkyl;

R_1 and R_2 are each independently H, alkyl, $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_aR_b$, $(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$, wherein at least one occurrence of R_1 and R_2 is $(CR_6R_7)_{n4}NR_aR_b$, $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$; or alternatively R_1, R_2 and the carbon atom they are connected to taken together form a 3-5 membered carbocycle;

R_4 is $(CR_6R_7)_{n4}(C=O)R_c$, $(C=O)(CR_6R_7)_{n4}R_c$, $(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}COOR_c$, $(CR_6R_7)_{n4}NR_c(C=O)R_d$, $(C=O)(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}SO_2R_c$, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted -cycloalkyl-alkyl;

each occurrence of R_5 is independently H, alkyl, cycloalkyl, or oxo;

or two R_5 groups taken together with the carbon atom(s) that they are connected to form a 3-7 membered optionally substituted saturated carbocycle;

or two R_5 groups are connected to different carbon atoms on the ring and taken together form a bond or an alkyl chain containing 1-3 carbons;

each occurrence of R_6 and R_7 are independently H, alkyl, or cycloalkyl;

each occurrence of R_a and R_b are independently H, alkyl, cycycloalkyl, saturated heterocycle, aryl, or heteroaryl; or alternatively R_a and R_b together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

each occurrence of R_c and R_d are independently H, alkyl, alkyl substituted by 1-4 substituents each of which is independently halogen, OR_8 or $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, or optionally substituted -cycloalkyl-alkyl; or alternatively R_c and R_d together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

each occurrence of R_8 is independently H, alkyl, or an optionally substituted heterocycle; or alternatively the two R_8 groups together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

R_9 is H, alkyl, halogen, or $(CR_6R_7)_{n4}OR_b$;

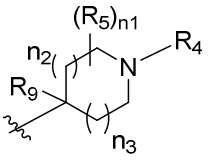
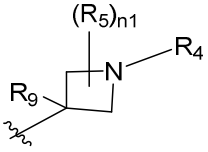
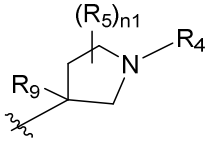
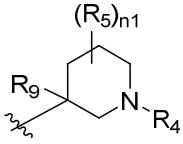
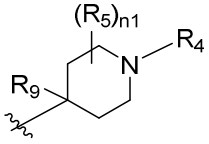
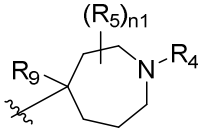
the alkyl, cycloalkyl, spiroalkyl, bicycloalkyl, heterocycle, aryl, and heteroaryl in R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_a, R_b, R_c, and R_d, where applicable, are optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, cycloalkyl, halogenated cycloalkyl, halogenated alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)C_{1-4}$alkyl, $(C=O)N(R_8)_2$, and oxo where valence permits;

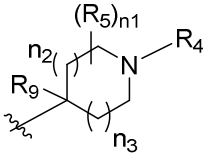
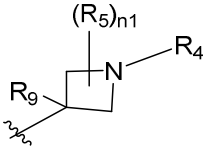
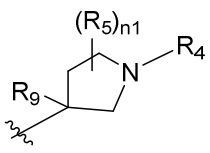
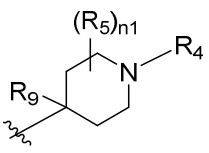
each occurrence of n_1 is independently an integer from 0-3 where valence permits;

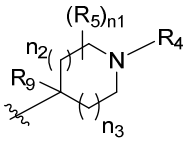
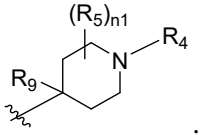
each occurrence of n_2 and n_3 is independently an integer that is 1, 2 or 0; and

each occurrence of n_4 is independently an integer from 0-3.

[0019] In any one of the examples described herein, each occurrence of n_2 and n_3 is independently an integer from 0-1.

[0020] In any one of the examples described herein, the structural motif  has the structure of , , , , or .

[0021] In any one of the examples described herein, the structural motif  has the structure of , , or .

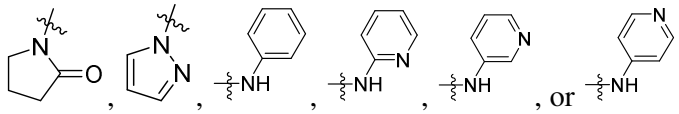
[0022] In any one of the examples described herein, the structural motif  has the structure of .

[0023] In any one of the examples described herein, at least one occurrence of R_1 and R_2 is H or alkyl.

[0024] In any one of the examples described herein, at least one occurrence of R_1 and R_2 is $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_aR_b$, $(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$.

[0025] In any one of the examples described herein, at least one occurrence of R_1 and R_2 is OR_a or NR_aR_b.

[0026] In any one of the examples described herein, R_1, R_2, and the carbon atom they are connected to taken together form a 3-5 membered carboncycle.

[0027] In any one of the examples described herein, R_1 and R_2 are each independently H, Me, OH, CH_2OH, NH_2, NHMe, NMe_2, CH_2NH_2, $CONH_2$, $CONHMe_2$, $CONMe_2$, NH(C=O)Me, NMe(C=O)Me, , or .

[0028] In any one of the examples described herein, R_4 is H, alkyl, halogenated alkyl, or cycloalkyl.

[0029] In any one of the examples described herein, R_4 is H, Me, or fluorinated ethyl.

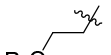
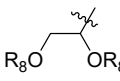
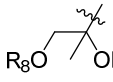
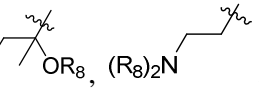
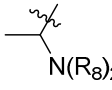
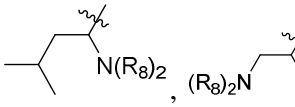
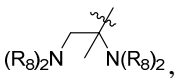
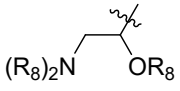
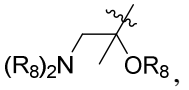
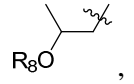
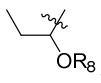
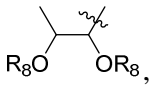
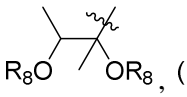
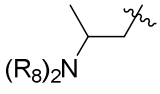
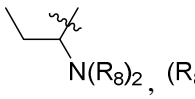
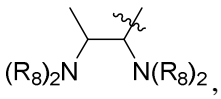
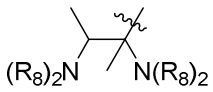
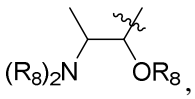
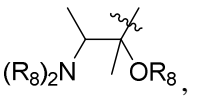
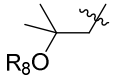
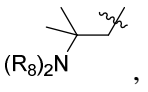
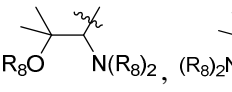
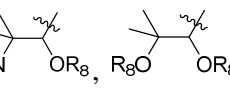
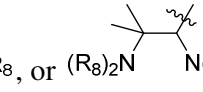
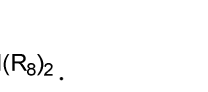
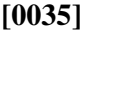
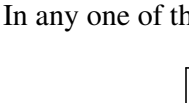
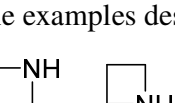
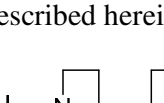
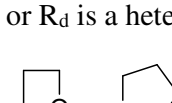
[0030] In any one of the examples described herein, R_4 is $(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}COR_c$, $(C=O)(CR_6R_7)_{n4}R_c$, $(CR_6R_7)_{n4}COOR_c$, $(CR_6R_7)_{n4}NR_c(C=O)R_d$, $(CR_6R_7)_{n4}(C=O)NR_cR_d$, $(CR_6R_7)_{n4}(C=O)(C=O)NR_cR_d$, $(C=O)(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}SO_2R_c$, or $(CR_6R_7)_{n4}SO_2NR_cR_d$.

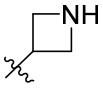
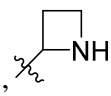
[0031] In any one of the examples described herein, R_4 is $(CR_6R_7)_2OR_c$, $(C=O)R_c$, $(C=O)(CR_6R_7)_{1\text{-}2}R_c$, $COOR_c$, $(CR_6R_7)_{1\text{-}2}NR_c(C=O)R_d$, $(C=O)NR_cR_d$, $(CR_6R_7)_{n4}(C=O)(C=O)NR_cR_d$, $(C=O)(CR_6R_7)_{1\text{-}2}OR_c$, SO_2R_c, or $SO_2NR_cR_d$.

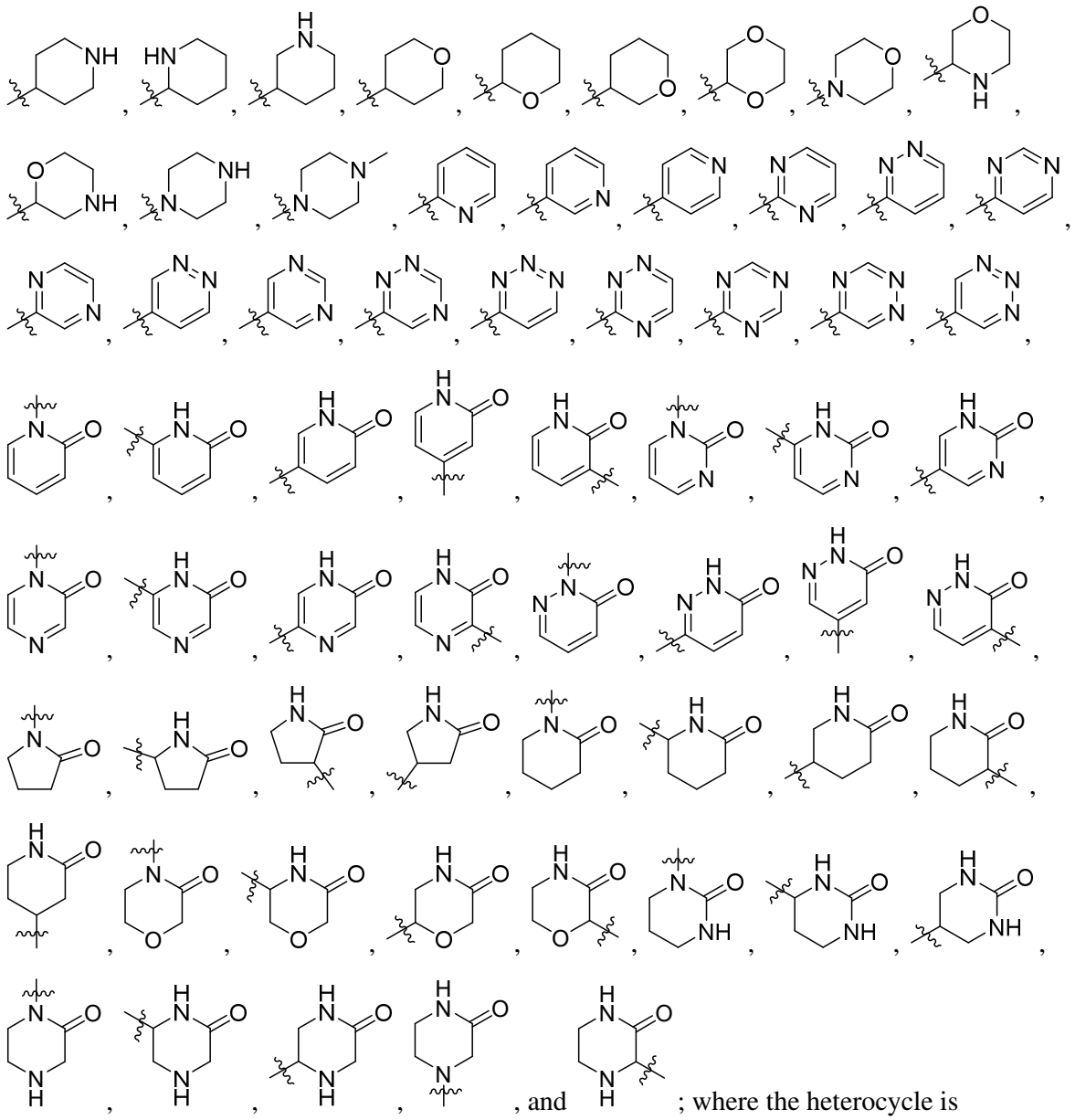
[0032] In any one of the examples described herein, R_4 is $(CH_2)_2OH$, $(CH_2)_2OMe$, (C=O)H, (C=O)Me, $(C=O)CH_2OH$, $(C=O)CH_2OMe$, (C=O)Et, (C=O)Ph, (C=O)isopropyl,

$(C=O)NH_2$, $(C=O)NHMe$, $(C=O)NMe_2$, $(C=O)CH_2NH_2$, $(C=O)CH_2NHMe$, $(C=O)CH(OH)CH_2OH$, $(C=O)CH(OMe)CH_2OH$, $(C=O)CH(OH)CH_2OMe$, $(C=O)(C=O)NMe_2$, $(C=O)OMe$, SO_2Me, SO_2Et, SO_2CH_2OH, SO_2CH_2OMe, SO_2NH_2, SO_2NHMe, or SO_2NMe_2.

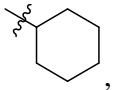
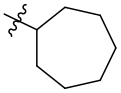
[0033] In any one of the examples described herein, R_4 is $(C=O)R_c$, $(C=O)(CR_6R_7)_{1-2}R_c$, $(C=O)(CR_6R_7)_{1-2}OR_c$, or SO_2R_c; and where R_c is selected from the group consisting of H, alkyl, alkyl substituted by 1-4 substituents each independently selected from the group consisting of halogen, OR_8 and $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, and optionally substituted -cycloalkyl-alkyl.

[0034] In any one of the examples described herein, R_c or R_d is H, Me, Et, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

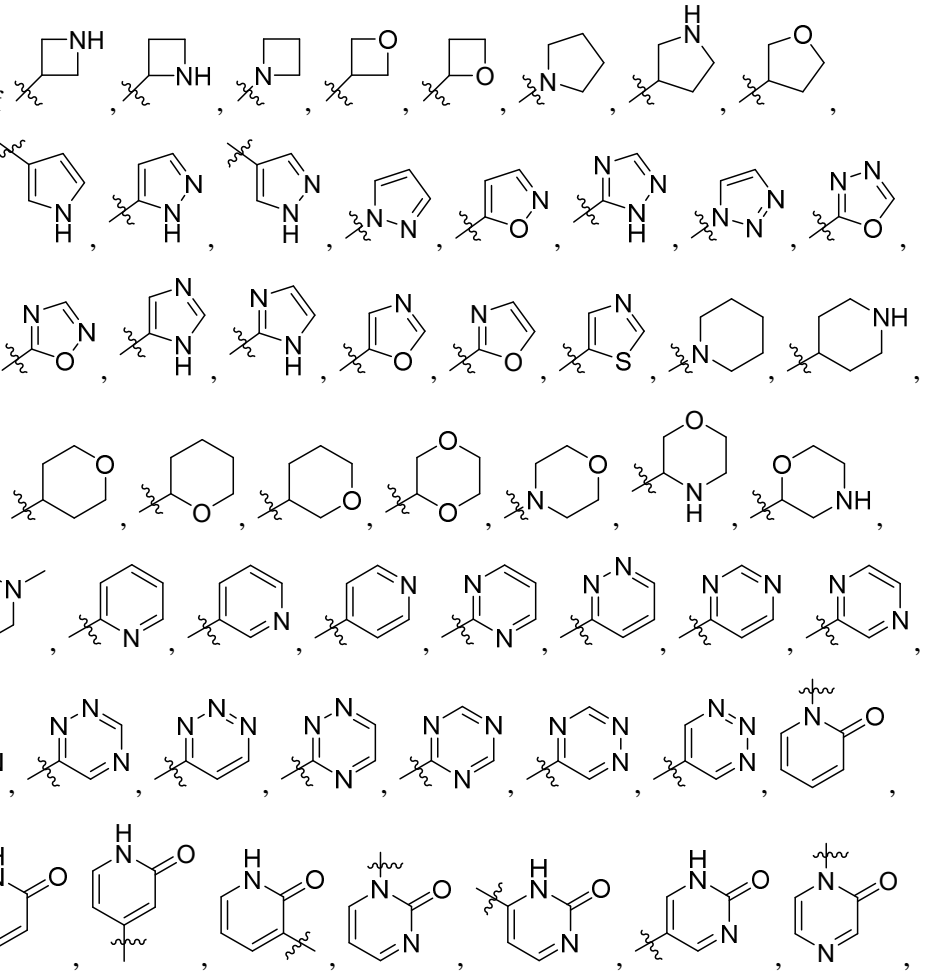
[0035] In any one of the examples described herein, R_c or R_d is a heterocycle selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , .

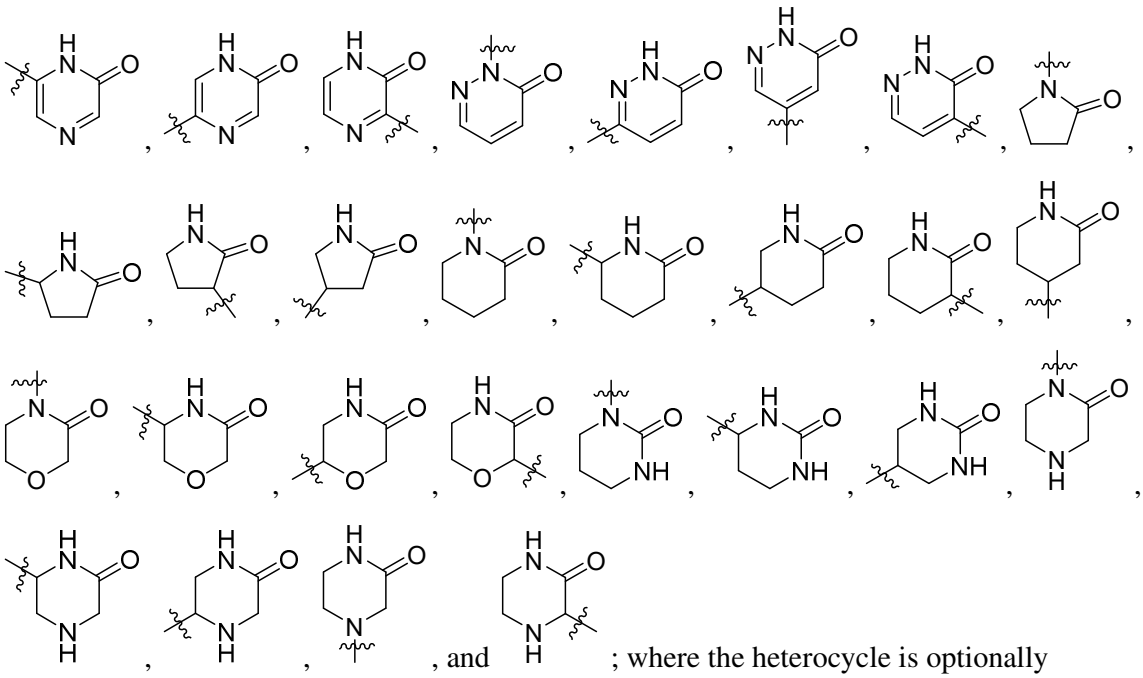

, and ; where the heterocycle is optionally substituted by one or more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits.

[0036] In any one of the examples described herein, R_c is cycloalkyl, spiroalkyl, or bicycloalkyl each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

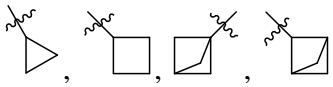
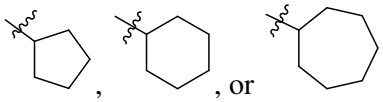
[0037] In any one of the examples described herein, R_c is , , , , , , or  each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

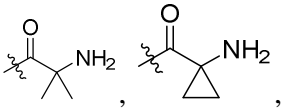
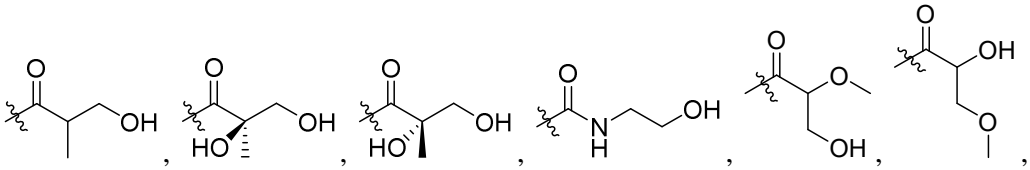
[0038] In any one of the examples described herein, R_4 is optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted cycloalkyl, optionally substituted -alkyl-cycloalkyl, or optionally substituted -cycloalkyl-alkyl.

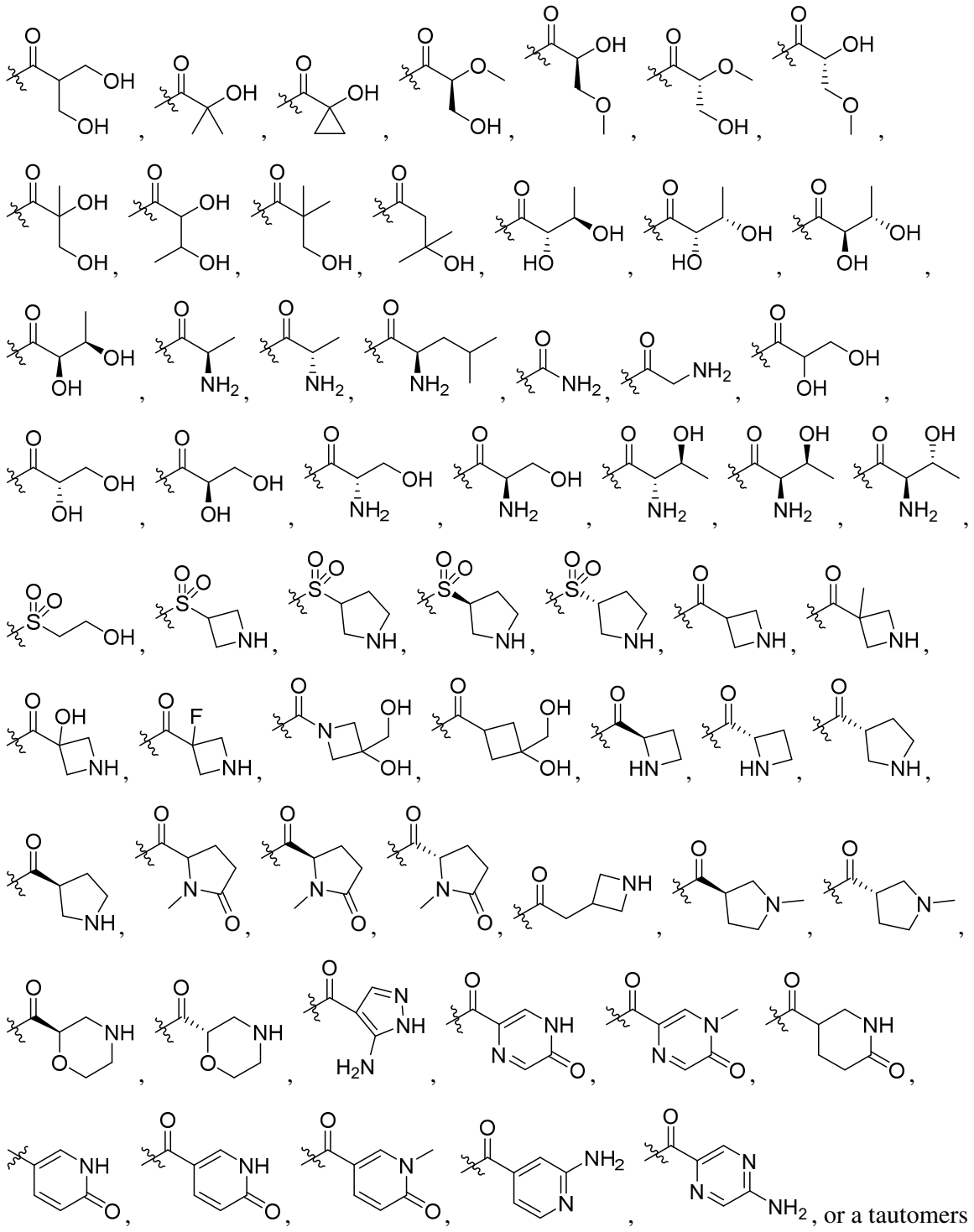
[0039] In any one of the examples described herein, R_4 is a heterocycle selected from the group consisting of 


, and ; where the heterocycle is optionally substituted by one or more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits.

[0040] In any one of the examples described herein, R_4 is cycloalkyl optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

[0041] In any one of the examples described herein, R_4 is 

, or each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

[0042] In any one of the examples described herein, R_4 is 



, or a tautomers thereof.

[0043] In any one of the examples described herein, at least one occurrence of R_5 is H, alkyl or cycloalkyl.

[0044] In any one of the examples described herein, at least one occurrence of R_5 is oxo.

[0045] In any one of the examples described herein, two R_5 groups are connected to different carbon atoms on the ring and taken together form a bond or an alkyl chain containing 1-3 carbons.

[0046] In any one of the examples described herein, two R_5 groups taken together with the carbon atom(s) that they are connected to form a 3-7 membered optionally substituted saturated carbocycle.

[0047] In any one of the examples described herein, at least one of R_a and R_b is independently H, alkyl, cycloalkyl, saturated heterocycle, aryl, or heteroaryl.

[0048] In any one of the examples described herein, R_a and R_b together with the nitrogen atom that they are connected to form an optionally substituted heterocycle including the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S.

[0049] In any one of the examples described herein, each occurrence of R_6 and R_7 are independently H or alkyl.

[0050] In any one of the examples described herein, R_9 is H, alkyl, or halogen.

[0051] In any one of the examples described herein, R_9 is $(CR_6R_7)_{n4}OR_b$.

[0052] In any one of the examples described herein, R_9 is H, F, or OH.

[0053] In any one of the examples described herein, Z is OR_a, NR_aR_b, or $NR_b(C=O)R_a$.

[0054] In any one of the examples described herein, Z is OH, OMe, NH_2, NHMe, or NMe_2.

[0055] In any one of the examples described herein, Z is OH.

[0056] In any one of the examples described herein, X_1 is H, halogen, fluorinated alkyl or alkyl.

[0057] In any one of the examples described herein, X_1 is H, F, Cl, Br, Me, CF_3, or CF_2Cl.

[0058] In any one of the examples described herein, X_1 is Me or Cl.

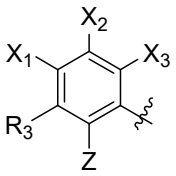
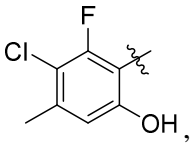
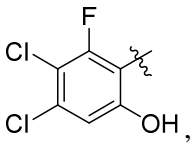
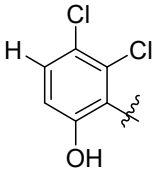
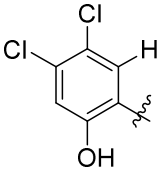
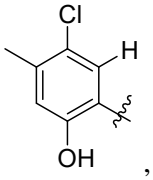
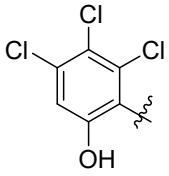
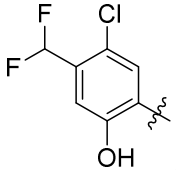
[0059] In any one of the examples described herein, X_2 is H, halogen, fluorinated alkyl or alkyl.

[0060] In any one of the examples described herein, X_2 is H, F, Cl, Br, Me, CF_3, or CF_2Cl.

[0061] In any one of the examples described herein, X_2 is Cl.

[0062] In any one of the examples described herein, X_3 is H, F, Cl, Br, fluorinated alkyl, or alkyl.

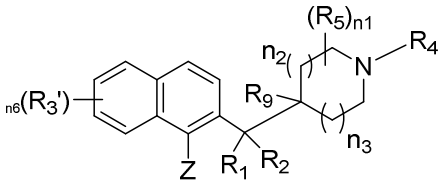
[0063] In any one of the examples described herein, X_3 is H, F, Cl, or CF_3.

[0064] In any one of the examples described herein, the structural moiety  has the structure of , , , , , , or , each of which is substituted by R_3.

[0065] In any one of the examples described herein, R_3 is H or alkyl.

[0066] In any one of the examples described herein, R_3 is halogen.

[0067] In any one of the examples described herein, the compound has a structure of Formula II,



II ;

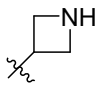
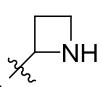
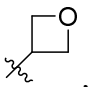
each occurrence of $R_{3'}$ is independently H, halogen, or alkyl; and

n_6 is an integer from 0-2.

[0068] In any one of the examples described herein, at least one occurrence of $R_{3'}$ is H or alkyl.

[0069] In any one of the examples described herein, at least one occurrence of $R_{3'}$ is halogen.

[0070] In any one of the examples described herein, at least one occurrence of R_8 is H, alkyl, or optionally substituted heterocycle.

[0071] In any one of the examples described herein, R_8 is H, Me, Et, Pr, Bu, or a heterocycle selected from the group consisting of , , , , ,

fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits.

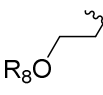
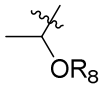
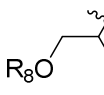
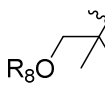
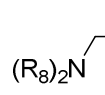
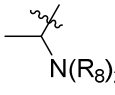
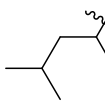
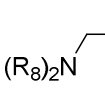
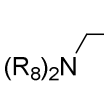
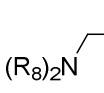
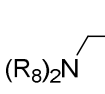
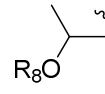
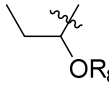
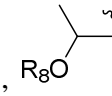
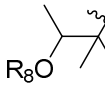
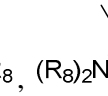
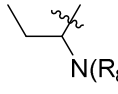
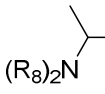
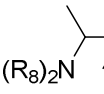
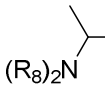
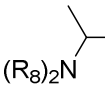
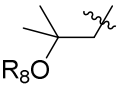
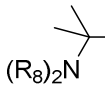
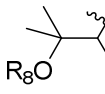
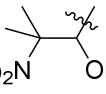
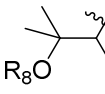
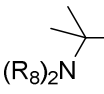
[0072] In any one of the examples described herein, the two R_8 groups together with the nitrogen atom that they are connected to form an optionally substituted heterocycle including the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S.

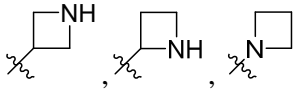
[0073] In any one of the examples described herein, n_1 is 0, 1, 2, or 3.

[0074] In any one of the examples described herein, n_4 is 0, 1, or 2.

[0075] In any one of the examples described herein, at least one occurrence of R_c or R_d is independently H, alkyl, alkyl substituted by 1-4 substituents each independently selected from the group consisting of halogen, OR_8 and $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, or optionally substituted -cycloalkyl-alkyl.

[0076] In any one of the examples described herein, R_c and R_d together with the nitrogen atom that they are connected to form an optionally substituted heterocycle including the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S.

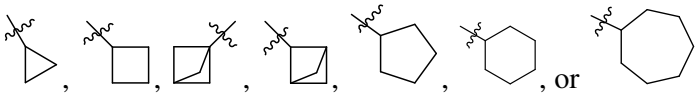
[0077] In any one of the examples described herein, at least one occurrence of R_c or R_d is independently H, Me, Et, , , , , , , , , , , , , , , , , , , , , , , , , , , or .

[0078] In any one of the examples described herein, at least one occurrence of R_c or R_d is independently a heterocycle selected from the group consisting of 

,

more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits.

[0079] In any one of the examples described herein, at least one occurrence of R_c or R_d is independently cycloalkyl, spiroalkyl, or bicycloalkyl each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

[0080] In any one of the examples described herein, at least one occurrence of R_c or R_d is independently , each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

[0081] In any one of the examples described herein, the compound is selected from a group consisting of compounds 1-338 in Table 1.

[0082] In another example, a pharmaceutical composition is described, including at least one compound according to any one of the examples described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

[0082a] In another aspect, there is provided a pharmaceutical composition comprising at least one compound as described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

[0083] In yet another example, a method of treating a condition in a mammalian species in need thereof is described, including administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of the examples described herein or a pharmaceutically acceptable salt thereof, where the condition is selected from the group consisting of cancer, an immunological disorder, a Central Nerve System (CNS) disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular disorder, and a kidney disease.

[0083a] In another aspect, there is provided a compound or a pharmaceutically acceptable salt thereof as described herein for use as a medicament.

[0083b] In another aspect, there is provided use of a a compound or a pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for treating a condition in a mammalian species in need thereof, wherein the condition is selected from the group consisting of cancer, an immunological disorder, a Central Nerve System (CNS) disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular

disorder, and a kidney disease;

optionally wherein the condition is:

(a) an immunological disorder that is transplant rejection or an autoimmune disease, wherein the autoimmune disease is optionally rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or Type I diabetes mellitus; or

(b) a Central Nerve System (CNS) disorder that is Alzheimer's disease;

(c) an inflammatory disorder that is an inflammatory skin condition, arthritis, psoriasis, spondylitis, parodontitits, or an inflammatory neuropathy;

(d) an gastroenterological disorder that is an inflammatory bowel disease; or

(e) a metabolic disorder that is obesity or Type II diabetes mellitus; or

(f) a cardiovascular disorder that is an ischemic stroke; or

(g) a kidney disease that is chronic kidney disease, nephritis, or chronic renal failure; or

(h) selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition, inflammatory neuropathy, psoriasis, spondylitis, parodontitis, Crohn's disease, ulcerative colitis, obesity, Type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof;

and optionally wherein the mammalian species is human.

[0084] In any one of the examples described herein, the immunological disorder is transplant rejection or an autoimmune disease.

[0085] In any one of the examples described herein, the autoimmune disease is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or Type I diabetes mellitus.

[0086] In any one of the examples described herein, the Central Nerve System (CNS) disorder is Alzheimer's disease.

[0087] In any one of the examples described herein, the inflammatory disorder is an inflammatory skin condition, arthritis, psoriasis, spondylitis, parodontitits, or an inflammatory neuropathy.

[0088] In any one of the examples described herein, the gastroenterological disorder is an inflammatory bowel disease.

[0089] In any one of the examples described herein, the metabolic disorder is obesity or Type II diabetes mellitus.

[0090] In any one of the examples described herein, the cardiovascular disorder is an ischemic stroke.

[0091] In any one of the examples described herein, the kidney disease is chronic kidney disease, nephritis, or chronic renal failure.

[0092] In any one of the examples described herein, the condition is selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition, inflammatory neuropathy, psoriasis, spondylitis, parodontitis, Crohn's disease, ulcerative colitis, obesity, Type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof.

[0093] In any one of the examples described herein, the mammalian species is human.

[0094] In yet another example, a method of blocking Kv1.3 potassium channel in a mammalian species in need thereof is described, including administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of the examples described herein or a pharmaceutically acceptable salt thereof.

[0095] In any one of the examples described herein, the mammalian species is human.

[0096] Any one of the examples disclosed herein may be properly combined with any other example disclosed herein. The combination of any one of the examples disclosed herein with any other examples disclosed herein is expressly contemplated. Specifically, the selection of one or more examples for one substituent group can be properly combined with the selection of one or more particular examples for any other substituent group. Such combination can be made in any one or more examples of the application described herein or any formula described herein.

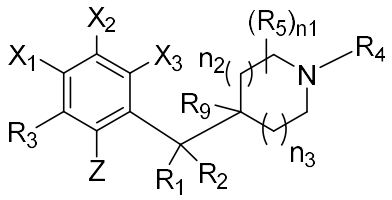
DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0097] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated. Unless

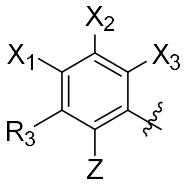
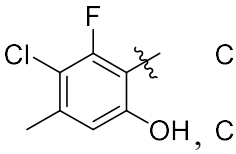
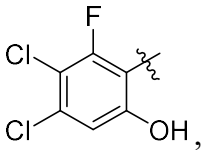
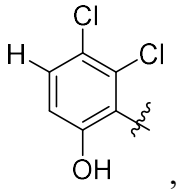
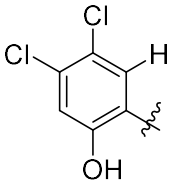
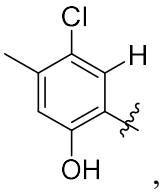
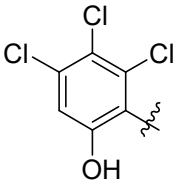
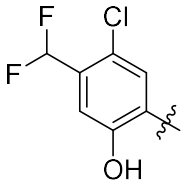
CLAIMS

1. A compound of Formula I or a pharmaceutically acceptable salt thereof,



I ;

wherein

the structural moiety  has the structure of  , , , , , or , each of which is substituted by R_3;

R_3 is H, halogen, or alkyl;

R_1 and R_2 are each independently H, alkyl, $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_aR_b$, $(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$, wherein at least one occurrence of R_1 and R_2 is $(CR_6R_7)_{n4}NR_aR_b$, $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$; or alternatively R_1, R_2 and the carbon atom they are connected to taken together form a 3-5 membered carbocycle;

R_4 is $(CR_6R_7)_{n4}(C=O)R_c$, $(C=O)(CR_6R_7)_{n4}R_c$, $(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}COOR_c$, $(CR_6R_7)_{n4}NR_c(C=O)R_d$, $(C=O)(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}SO_2R_c$, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted -cycloalkyl-alkyl;

each occurrence of R_5 is independently H, alkyl, cycloalkyl, or oxo;

or two R_5 groups taken together with the carbon atom(s) that they are connected to form a 3-7 membered optionally substituted saturated carbocycle;

or two R_5 groups are connected to different carbon atoms on the ring and taken together form a bond or an alkyl chain containing 1-3 carbons;

each occurrence of R_6 and R_7 are independently H, alkyl, or cycloalkyl;

each occurrence of R_a and R_b are independently H, alkyl, cycycloalkyl, saturated heterocycle, aryl, or heteroaryl; or alternatively R_a and R_b together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

each occurrence of R_c and R_d are independently H, alkyl, alkyl substituted by 1-4 substituents each of which is independently halogen, OR_8 or $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, or optionally substituted -cycloalkyl-alkyl; or alternatively R_c and R_d together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

each occurrence of R_8 is independently H, alkyl, or an optionally substituted heterocycle; or alternatively the two R_8 groups together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S;

R_9 is H, alkyl, halogen, or $(CR_6R_7)_{n4}OR_b$;

the alkyl, cycloalkyl, spiroalkyl, bicycloalkyl, heterocycle, aryl, and heteroaryl in R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_a, R_b, R_c, and R_d, where applicable, are optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, cycloalkyl, halogenated cycloalkyl, halogenated alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)C_{1-4}$alkyl, $(C=O)N(R_8)_2$, and oxo where valence permits;

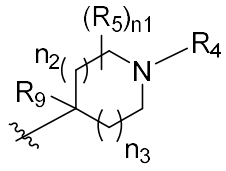
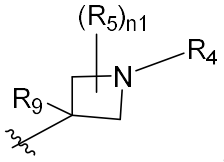
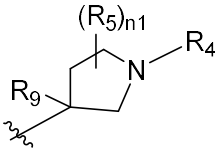
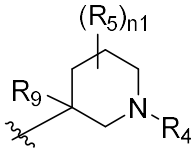
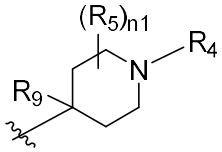
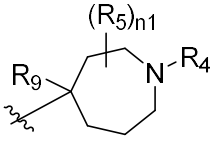
each occurrence of n_1 is independently an integer from 0-3 where valence permits;

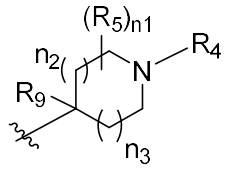
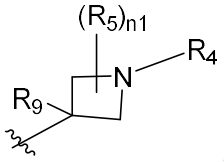
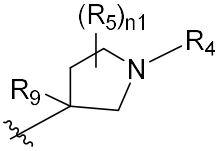
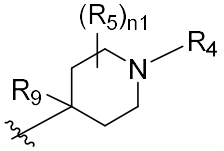
each occurrence of n_2 and n_3 is independently an integer that is 1, 2 or 0; and

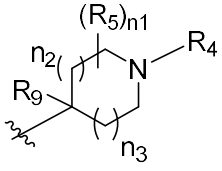
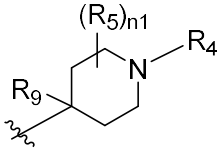
each occurrence of n_4 is independently an integer from 0-3.

2. The compound or a pharmaceutically acceptable salt thereof of claim 1, wherein:

(a) each occurrence of n_2 and n_3 is independently an integer from 0-1; or

(b) the structural motif  has the structure of , , , , or ; or

(c) the structural motif  has the structure of , , or .

3. The compound or a pharmaceutically acceptable salt thereof of claim 1 or 2, wherein the structural motif  has the structure of .

4. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein at least one occurrence of R_1 and R_2 is $(CR_6R_7)_{n4}OR_a$, $(CR_6R_7)_{n4}NR_aR_b$,

$(CR_6R_7)_{n4}NR_a(C=O)R_b$, $(CR_6R_7)_{n4}NR_aSO_2R_b$, or $(CR_6R_7)_{n4}CONR_aR_b$.

5. The compound or a pharmaceutically acceptable salt thereof of claim 4, wherein at least one occurrence of R_1 and R_2 is OR_a or NR_aR_b.

6. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein R_1, R_2, and the carbon atom they are connected to taken together form a 3-5 membered carbocycle.

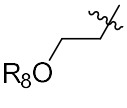
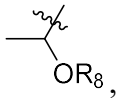
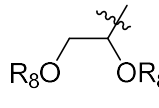
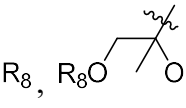
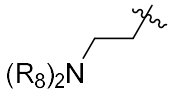
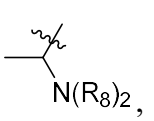
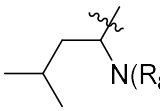
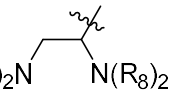
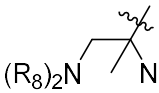
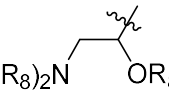
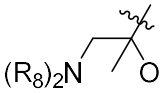
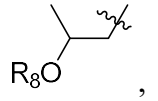
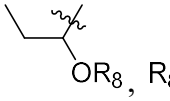
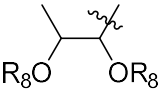
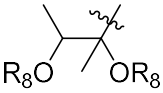
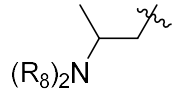
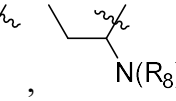
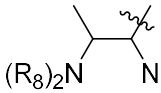
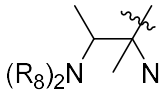
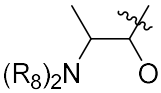
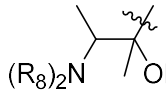
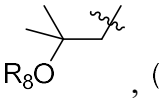
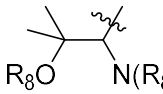
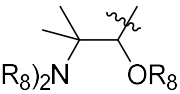
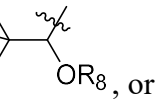
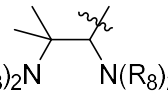
7. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-6, wherein R_4 is $(CR_6R_7)_{n4}OR_c$, $(CR_6R_7)_{n4}COR_c$, $(C=O)(CR_6R_7)_{n4}R_c$, $(CR_6R_7)_{n4}COOR_c$, $(CR_6R_7)_{n4}NR_c(C=O)R_d$, $(C=O)(CR_6R_7)_{n4}OR_c$, or $(CR_6R_7)_{n4}SO_2R_c$.

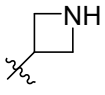
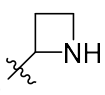
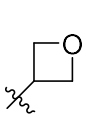
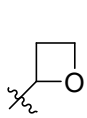
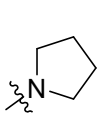
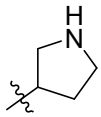
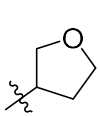
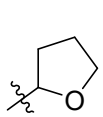
8. The compound or a pharmaceutically acceptable salt thereof of claim 7, wherein R_4 is $(CR_6R_7)_2OR_c$, $(C=O)R_c$, $(C=O)(CR_6R_7)_{1-2}R_c$, $COOR_c$, $(CR_6R_7)_{1-2}NR_c(C=O)R_d$, $(C=O)(CR_6R_7)_{1-2}OR_c$, or SO_2R_c.

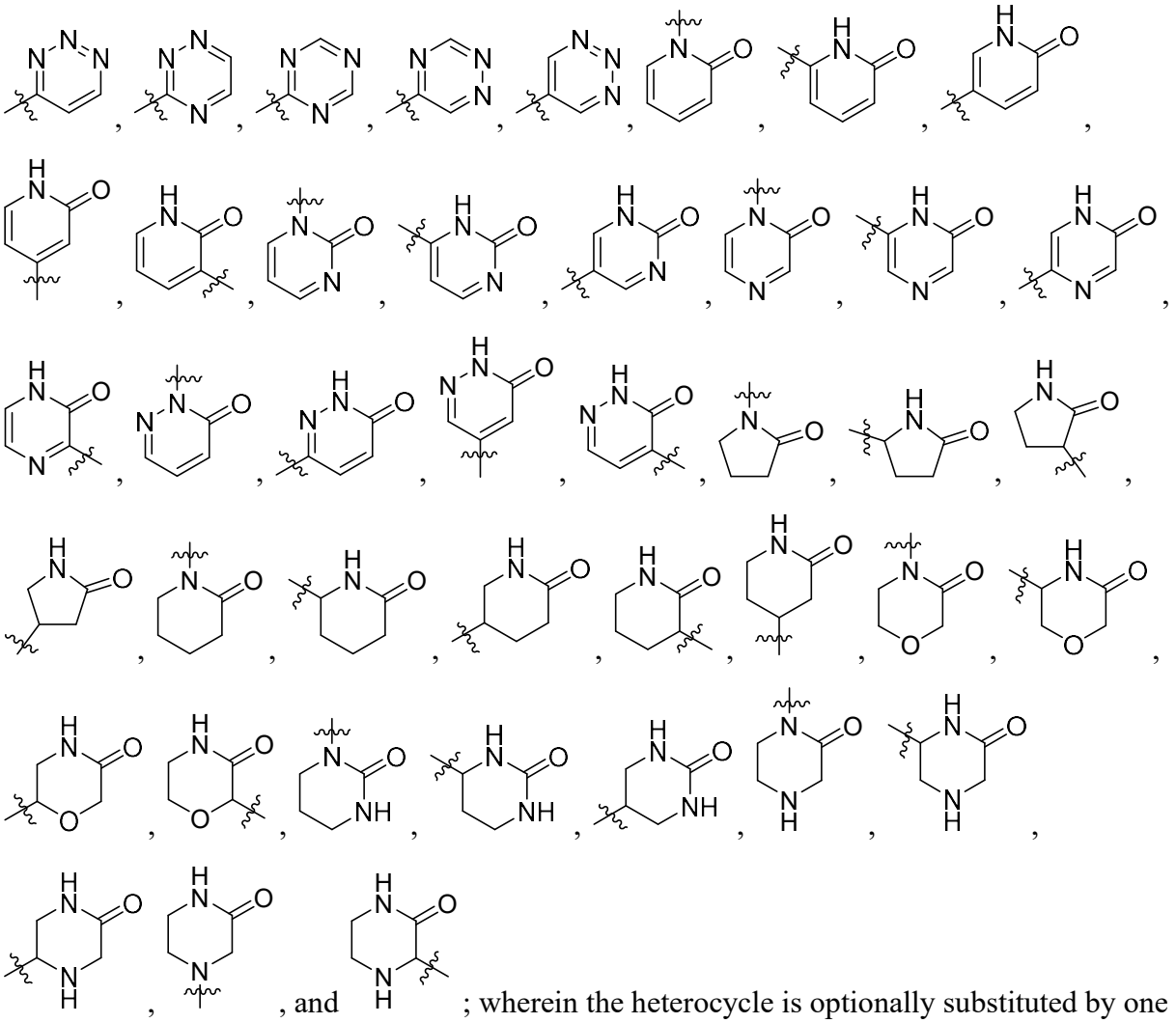
9. The compound or a pharmaceutically acceptable salt thereof of claim 8, wherein R_4 is $(CH_2)_2OH$, $(CH_2)_2OMe$, $(C=O)H$, $(C=O)Me$, $(C=O)CH_2OH$, $(C=O)CH_2OMe$, $(C=O)Et$, $(C=O)Ph$, $(C=O)$isopropyl, $(C=O)CH_2NH_2$, $(C=O)CH_2NHMe$, $(C=O)CH(OH)CH_2OH$, $(C=O)CH(OMe)CH_2OH$, $(C=O)CH(OH)CH_2OMe$, $(C=O)OMe$, SO_2Me, SO_2Et, SO_2CH_2OH, or SO_2CH_2OMe.

10. The compound or a pharmaceutically acceptable salt thereof of claim 8, wherein R_4 is $(C=O)R_c$, $(C=O)(CR_6R_7)_{1-2}R_c$, $(C=O)(CR_6R_7)_{1-2}OR_c$, or SO_2R_c; and wherein R_c is selected from the group consisting of H, alkyl, alkyl substituted by 1-4 substituents each independently selected from the group consisting of halogen, OR_8 and $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, and optionally substituted -cycloalkyl-alkyl.

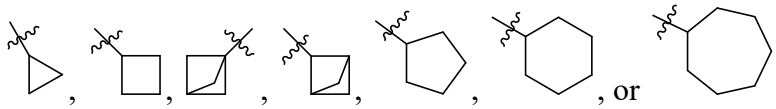
11. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-6, wherein R_4 is $(CR_6R_7)_2OR_c$, $(C=O)R_c$, $(C=O)(CR_6R_7)_{1-2}R_c$, $COOR_c$, $(CR_6R_7)_{1-2}NR_c(C=O)R_d$, $(C=O)(CR_6R_7)_{1-2}OR_c$, or SO_2R_c, and:

(a) R_c or R_d is H, Me, Et, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or ; or

(b) R_c or R_d is a heterocycle selected from the group consisting of , , , , , , , , , .

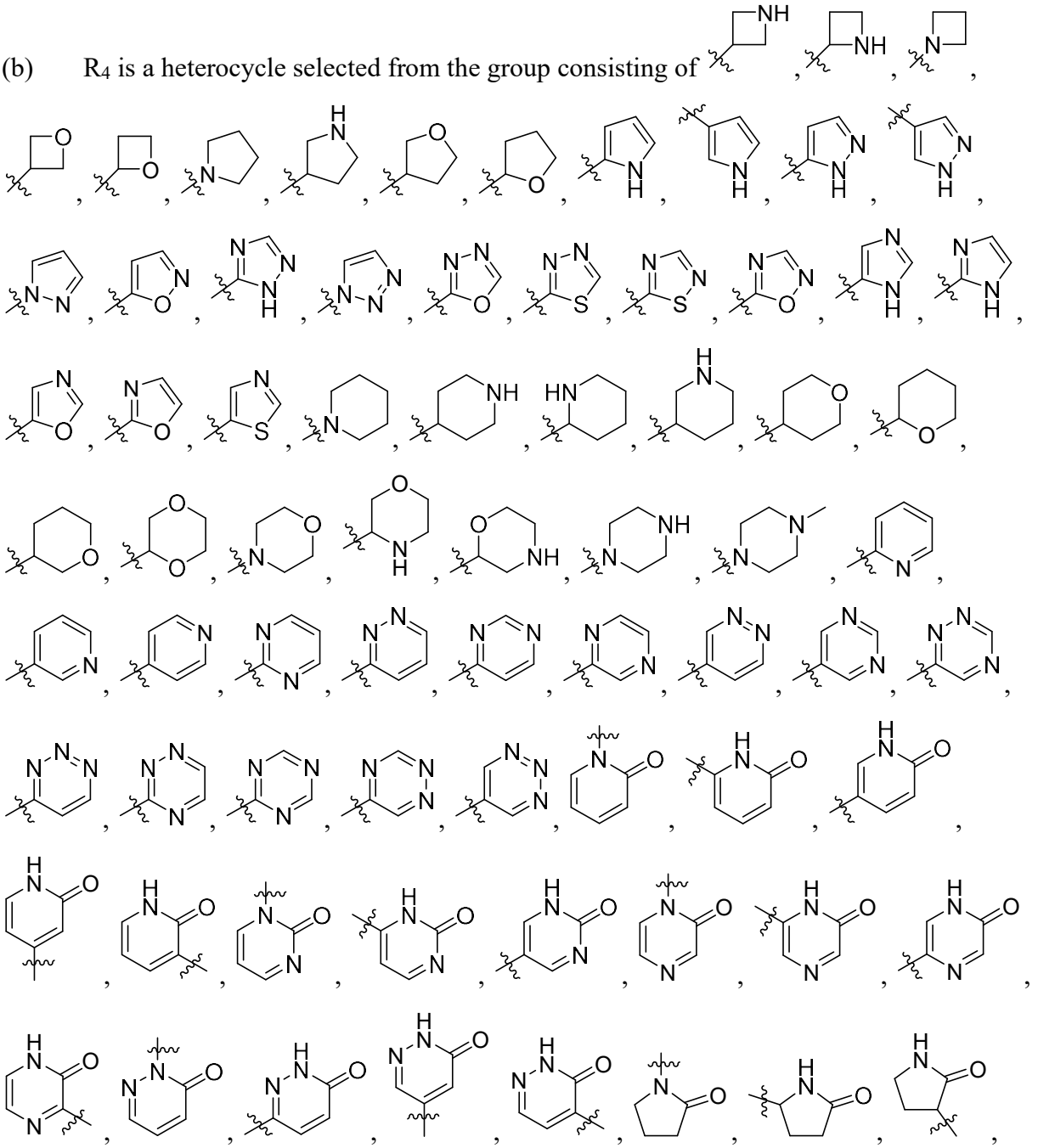

; wherein the heterocycle is optionally substituted by one or more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1\text{-}4}$alkyl where valence permits; or

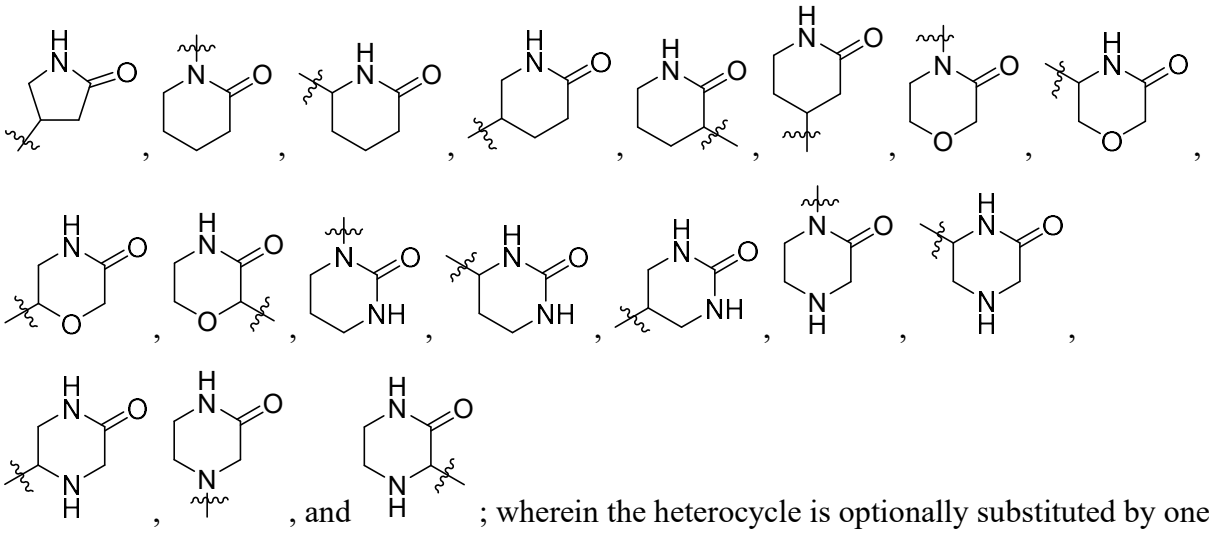
(c) R_c is cycloalkyl, spiroalkyl, or bicycloalkyl each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0\text{-}2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits; or

(d) R_c is  each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0\text{-}2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

12. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-6, wherein:

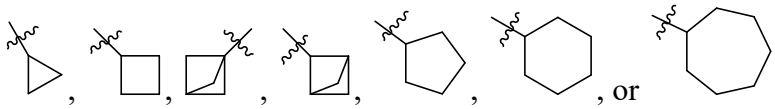
(a) R_4 is optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted -cycloalkyl-alkyl; or

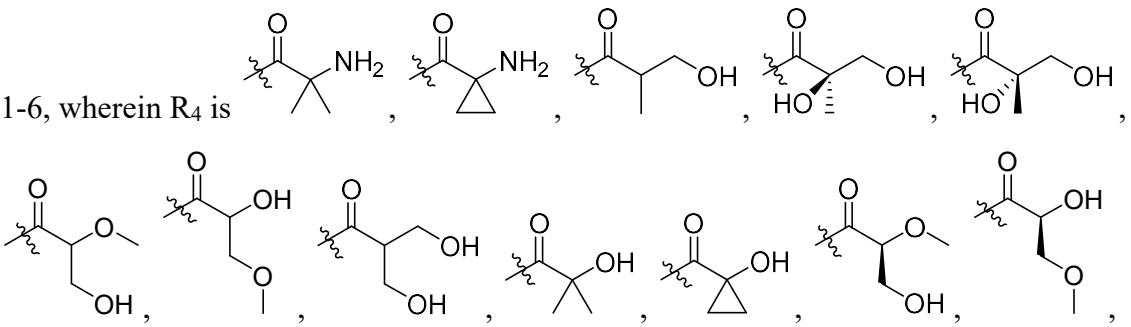
(b) R_4 is a heterocycle selected from the group consisting of 

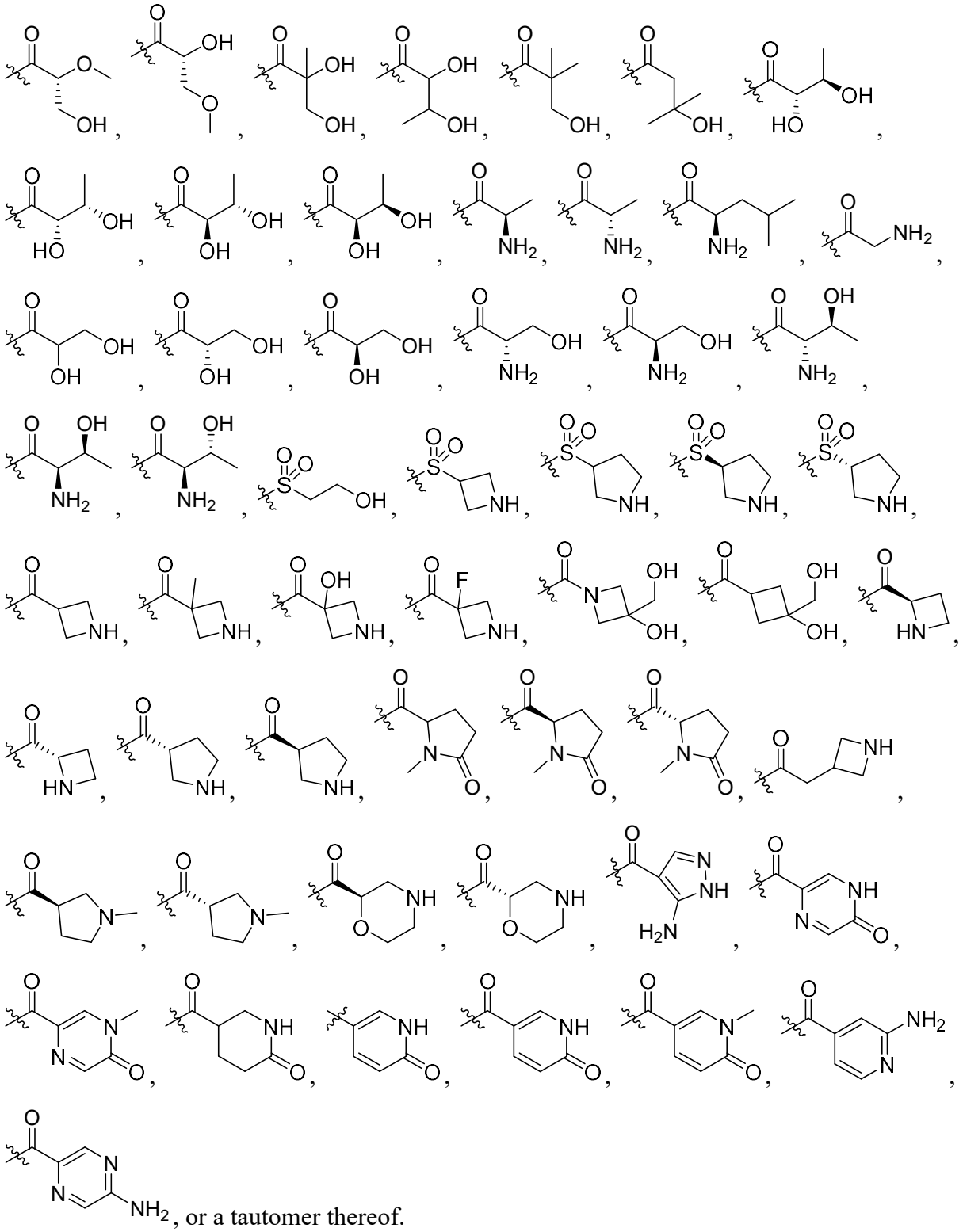


; wherein the heterocycle is optionally substituted by one or more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits; or

(c) R_4 is cycloalkyl optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits; or

(d) R_4 is  each optionally substituted by 1-4 substituents each independently selected from the group consisting of alkyl, halogen, CN, $-(CH_2)_{0-2}OR_8$, $N(R_8)_2$, $(C=O)N(R_8)_2$, and oxo where valence permits.

13. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-6, wherein R_4 is 



, or a tautomer thereof.

14. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein:

(a) at least one occurrence of R_5 is H, alkyl or cycloalkyl; or

(b) at least one occurrence of R_5 is oxo; or

(c) two R_5 groups are connected to different carbon atoms on the ring and taken together form a bond or an alkyl chain containing 1-3 carbons; or

(d) two R_5 groups taken together with the carbon atom(s) that they are connected to form a 3-7 membered optionally substituted saturated carbocycle.

15. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-14, wherein:

(a) at least one of R_a and R_b is independently H, alkyl, cycloalkyl, saturated heterocycle, aryl, or heteroaryl; or

(b) R_a and R_b together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S.

16. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-15, wherein:

(a) each occurrence of R_6 and R_7 are independently H or alkyl; and/or

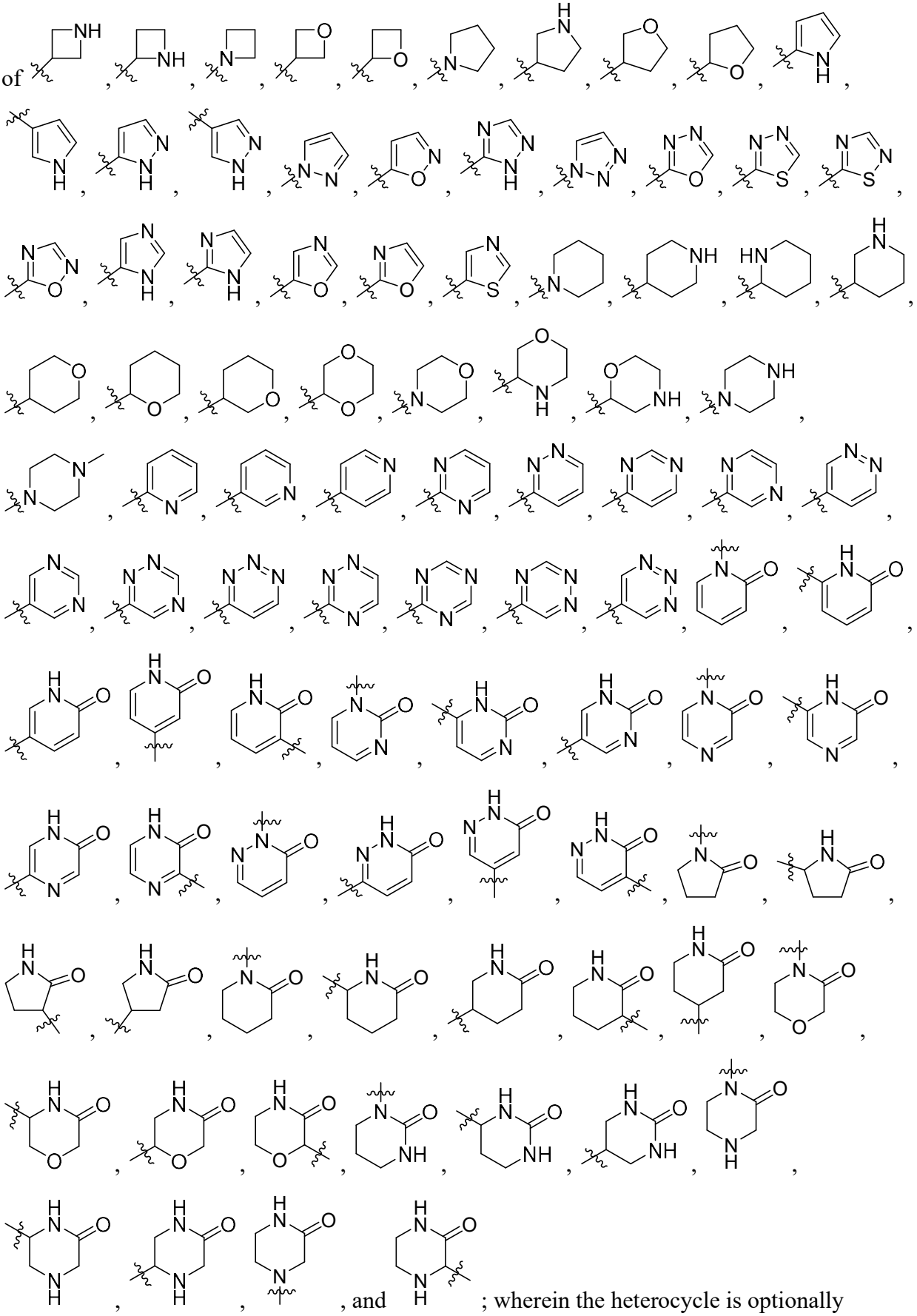
(b) R_9 is (i) H, alkyl, or halogen, or (ii) $(CR_6R_7)_{n4}OR_b$; or (iii) H, F, or OH.

17. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-16, wherein R_3 is H or alkyl.

18. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-16, wherein R_3 is halogen.

19. The compound or a pharmaceutically acceptable salt thereof of any one of claims 1-18, wherein:

(a) at least one occurrence of R_8 is H, alkyl, or optionally substituted heterocycle, optionally wherein R_8 is H, Me, Et, Pr, Bu, or a heterocycle selected from the group consisting

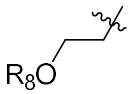
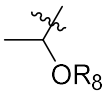
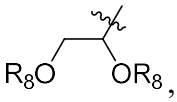
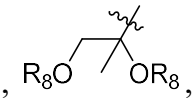
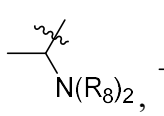
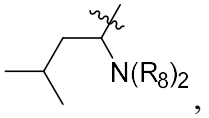
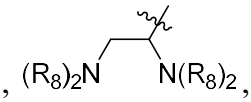
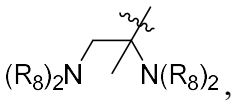
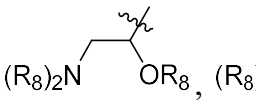
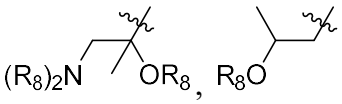
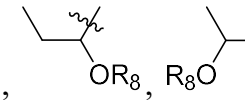
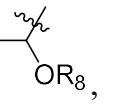
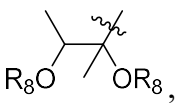
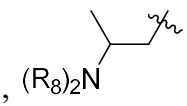
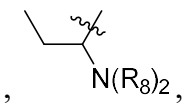
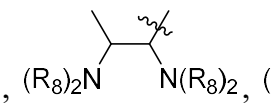
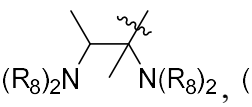
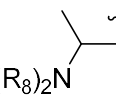
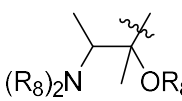
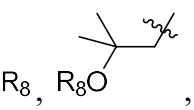
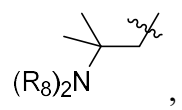
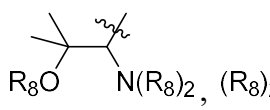
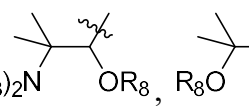
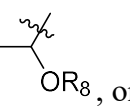
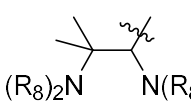
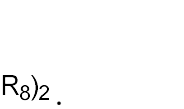
of ; wherein the heterocycle is optionally

substituted by one or more cyano, cycloalkyl, fluorinated alkyl, fluorinated cycloalkyl, halogen, OH, NH_2, oxo, or $(C=O)C_{1-4}$alkyl where valence permits; or

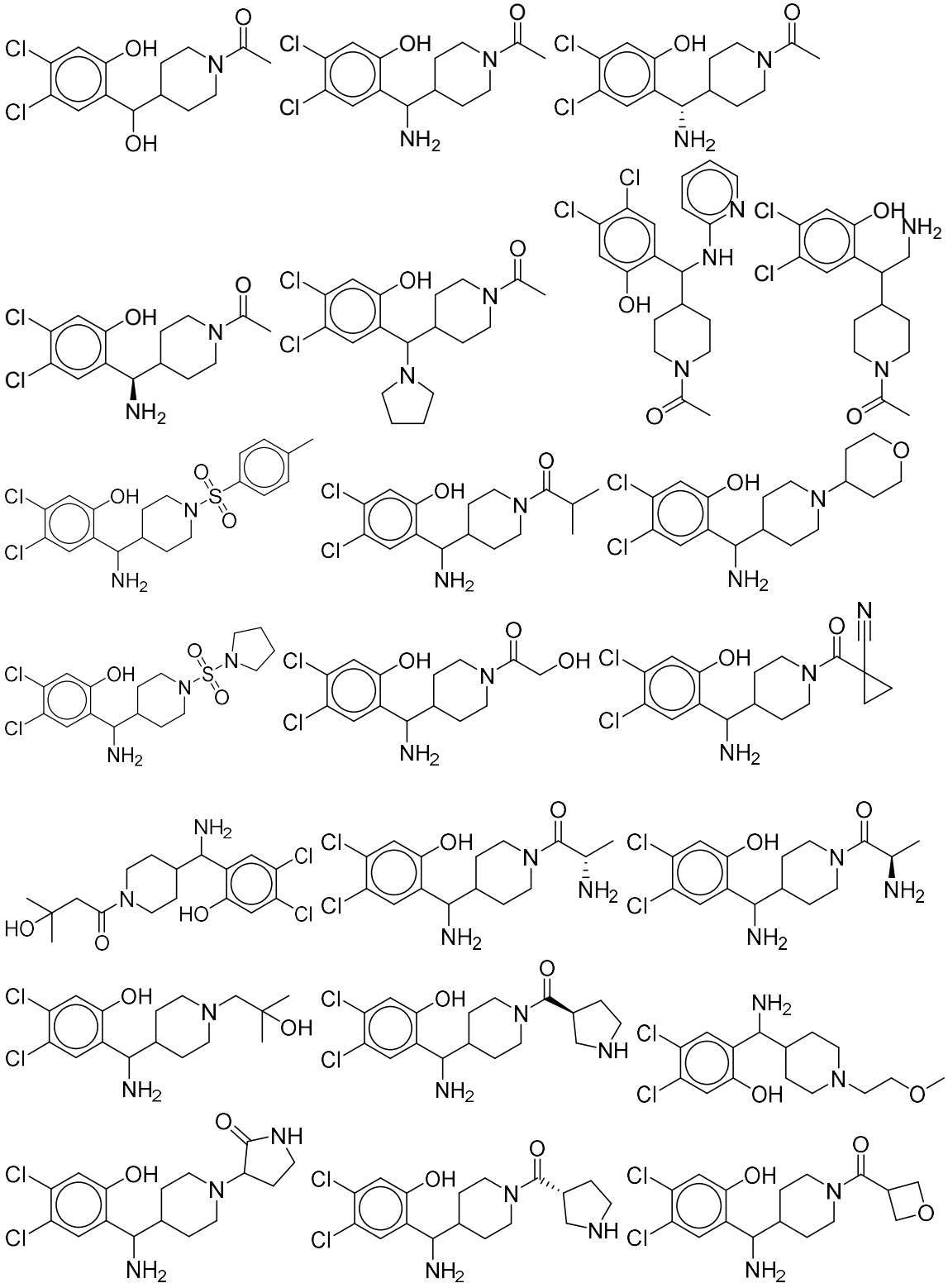
(b) the two R_8 groups together with the nitrogen atom that they are connected to form an optionally substituted heterocycle comprising the nitrogen atom and 0-3 additional heteroatoms each selected from the group consisting of N, O, and S.

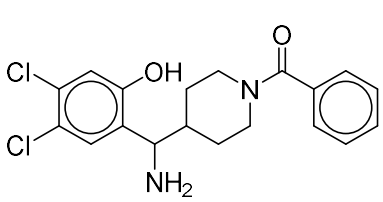
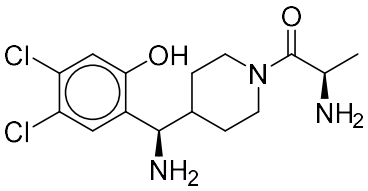
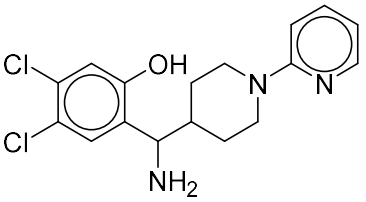
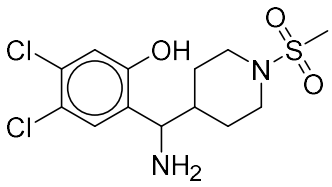
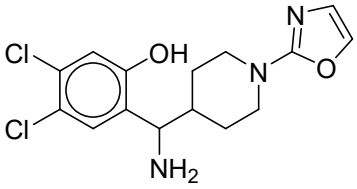
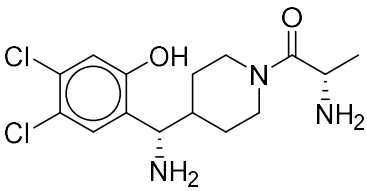
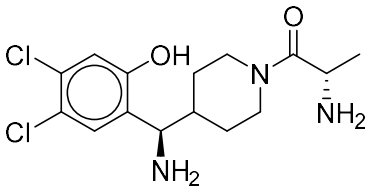
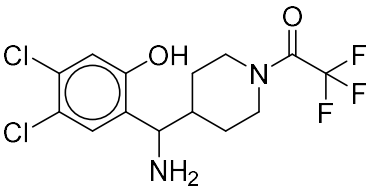
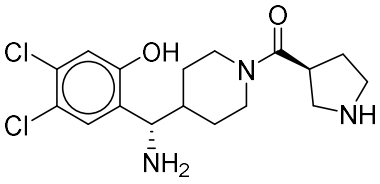
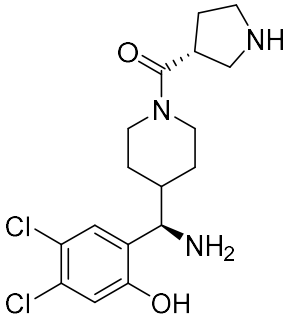
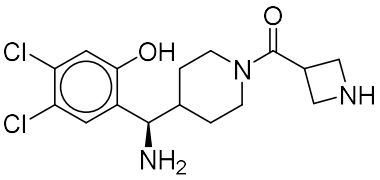
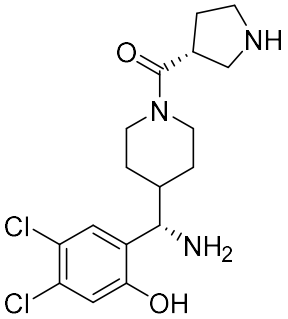
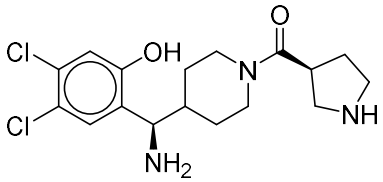
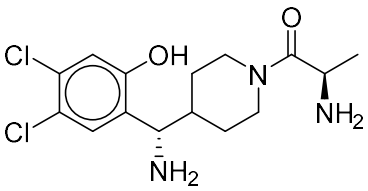
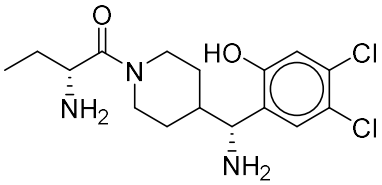
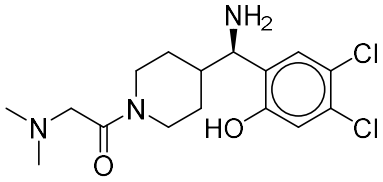
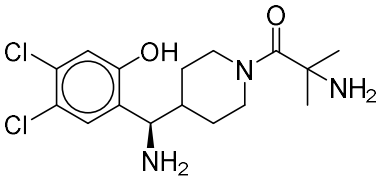
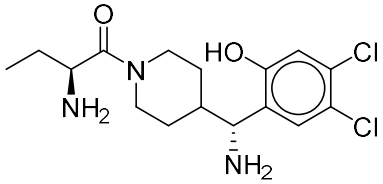
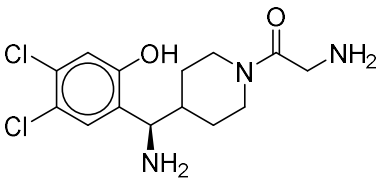
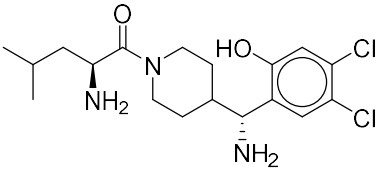
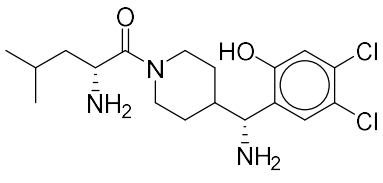
20. The compound or a pharmaceutically acceptable salt thereof of any one of claim 1-6, wherein:

(a) at least one occurrence of R_c or R_d is independently H, alkyl, alkyl substituted by 1-4 substituents each independently selected from the group consisting of halogen, OR_8 and $N(R_8)_2$, alkenyl, optionally substituted cycloalkyl, optionally substituted bicycloalkyl, optionally substituted spiroalkyl, optionally substituted saturated heterocycle, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted -alkyl-aryl, optionally substituted -alkyl-heteroaryl, optionally substituted -alkyl-heterocycle, optionally substituted -alkyl-cycloalkyl, or optionally substituted -cycloalkyl-alkyl; or

(b) at least one occurrence of R_c or R_d is independently H, Me, Et, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

21. The compound or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is selected from the group consisting of the following compounds and pharmaceutically acceptable salts thereof



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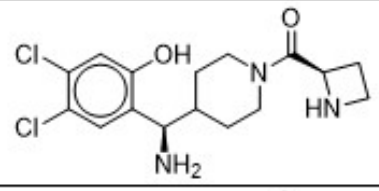
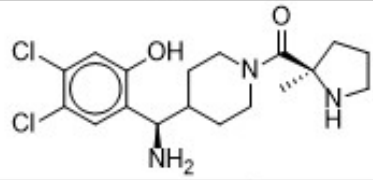
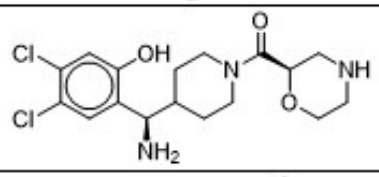
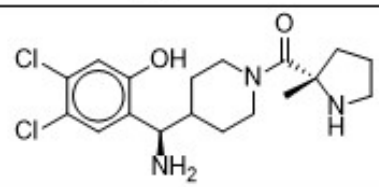
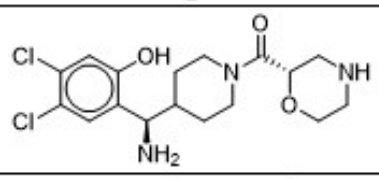
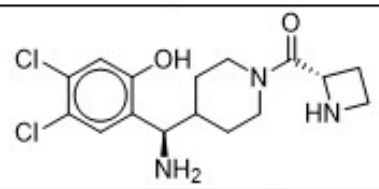
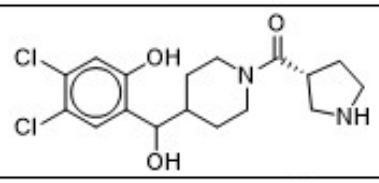
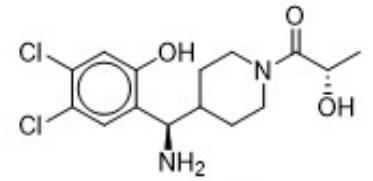
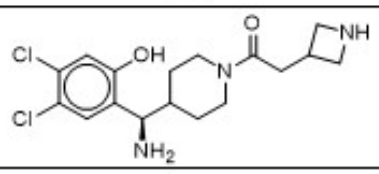

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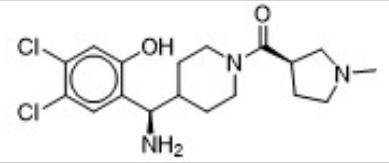
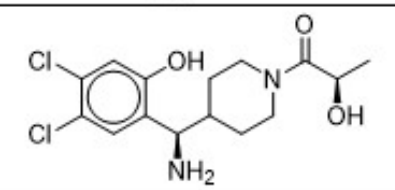
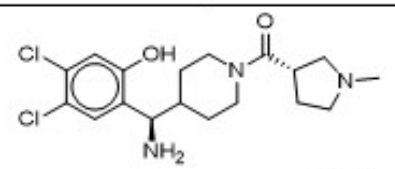
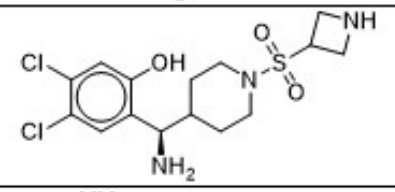
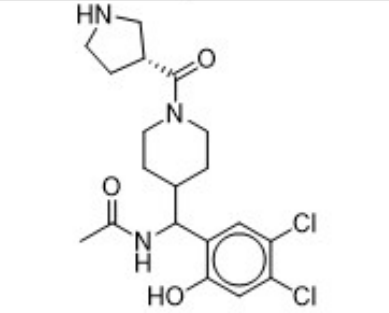
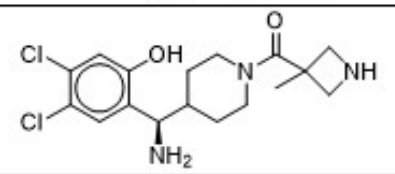
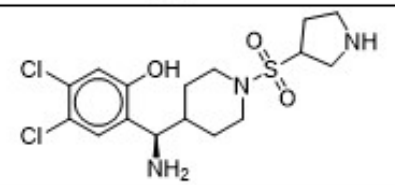
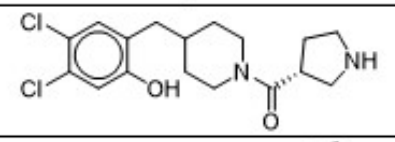
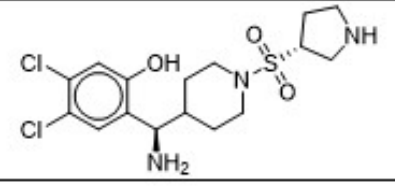

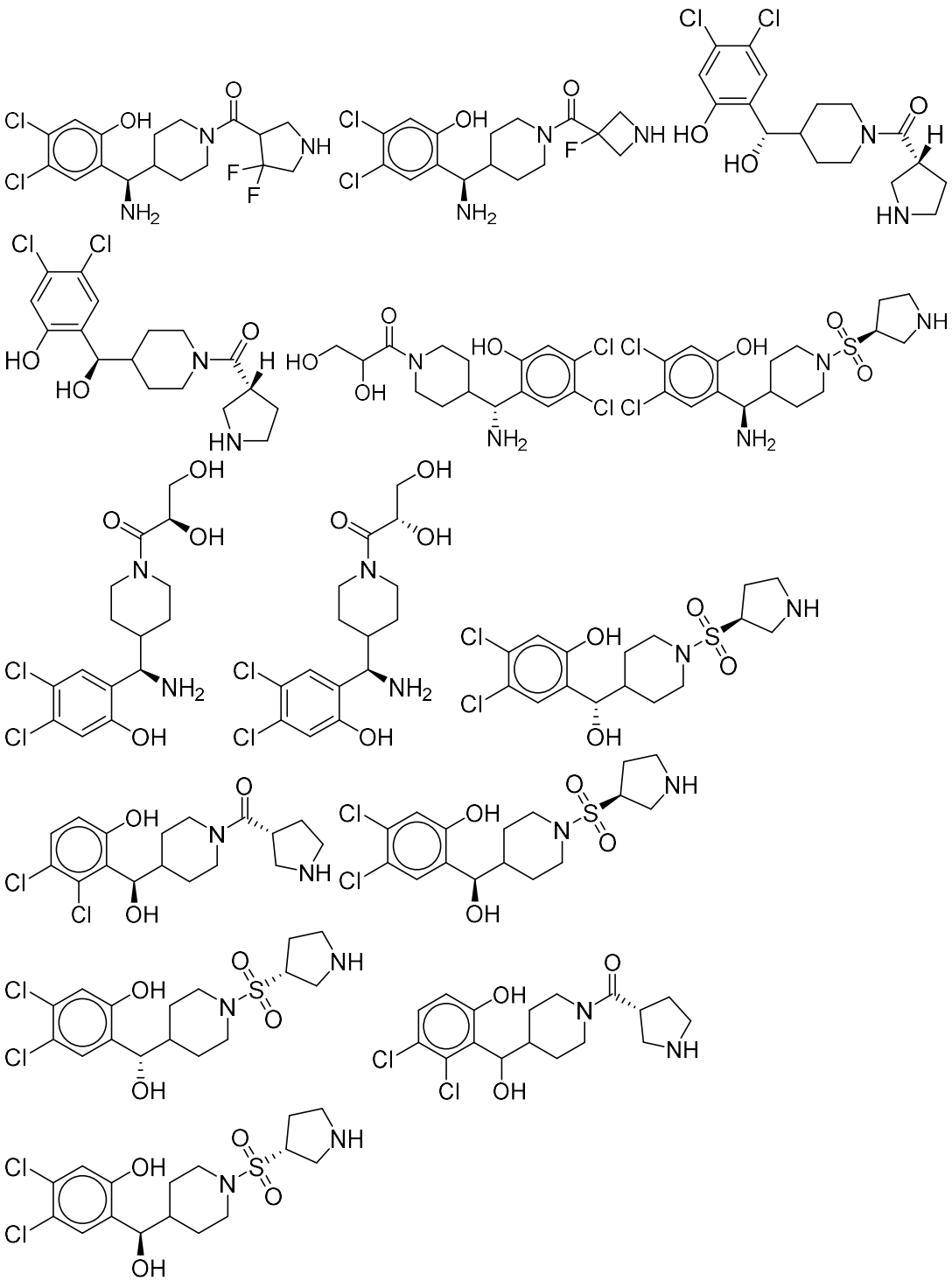

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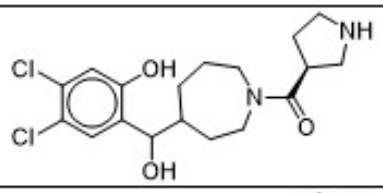
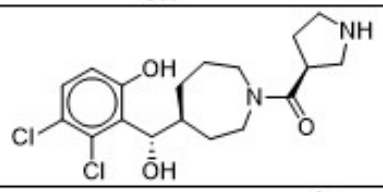
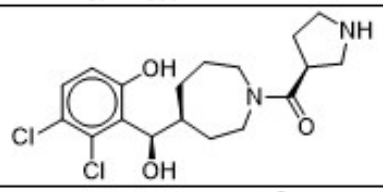
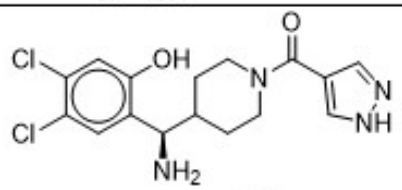
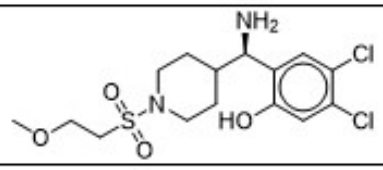
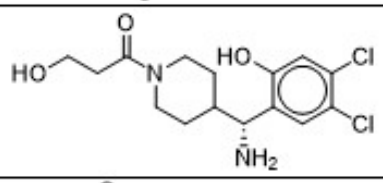
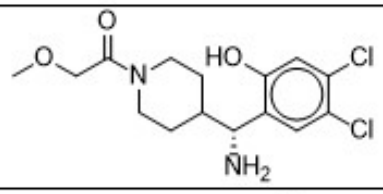
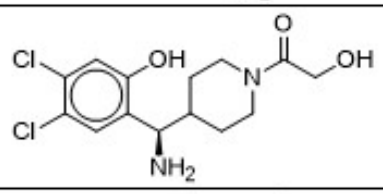
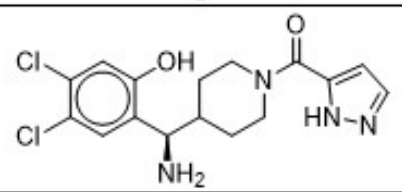

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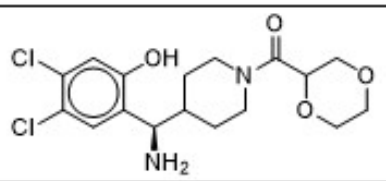
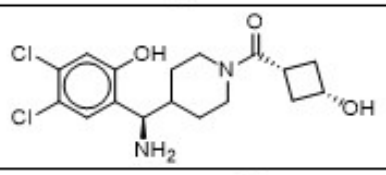
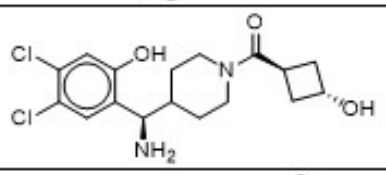
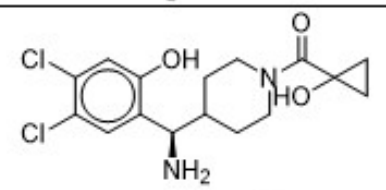
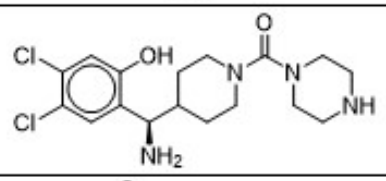
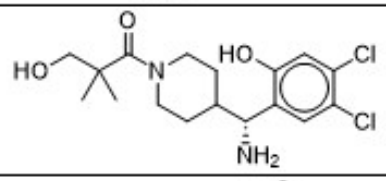
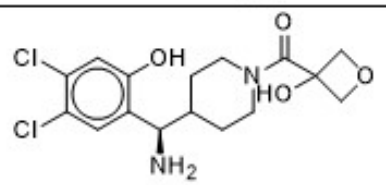
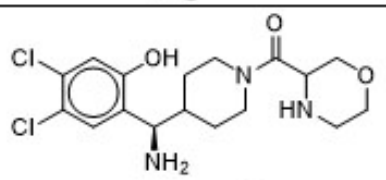
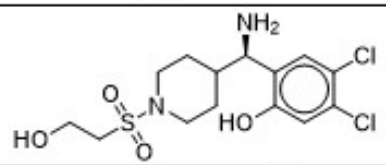
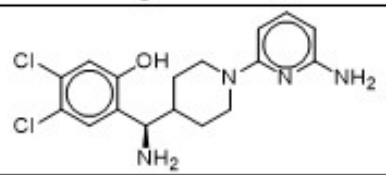

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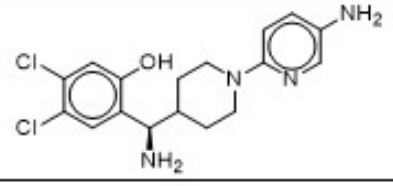
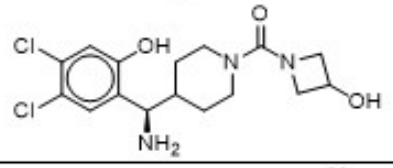
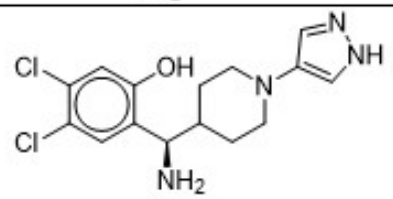
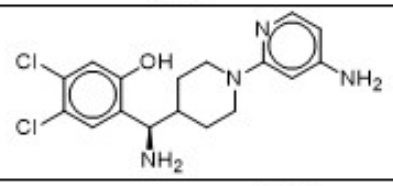
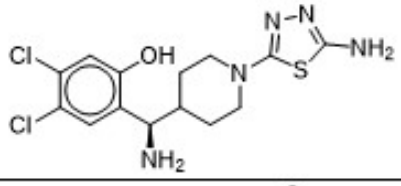
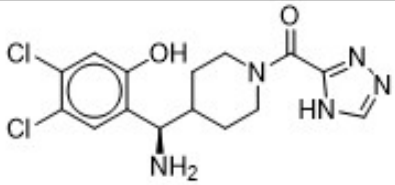
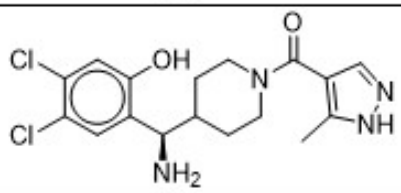
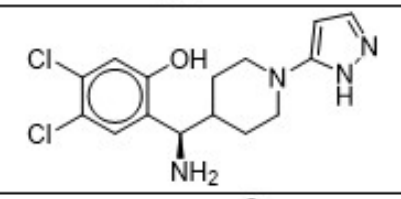
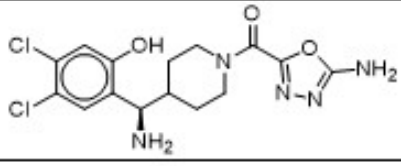

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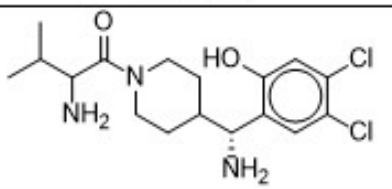
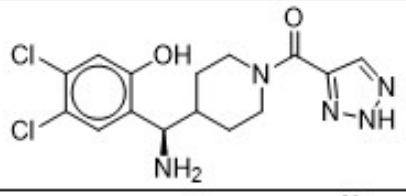
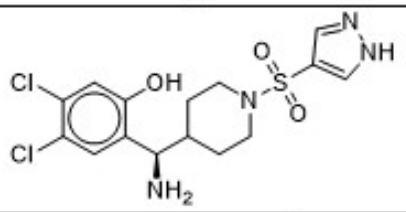
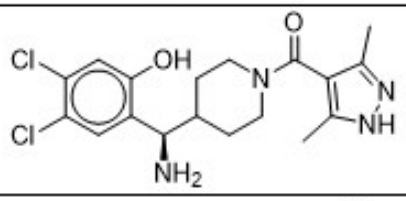
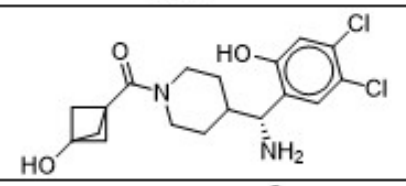
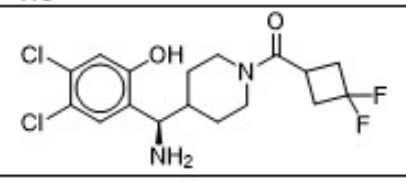
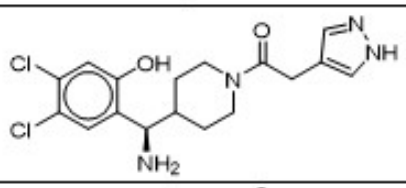
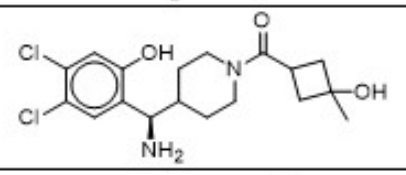
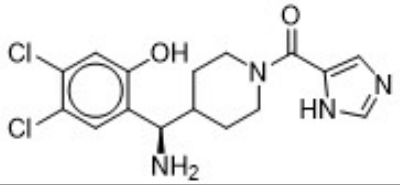

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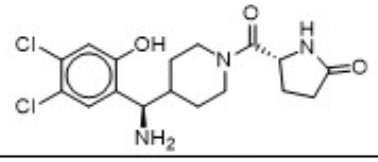
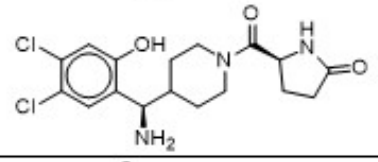
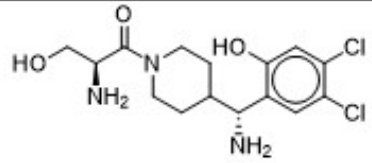
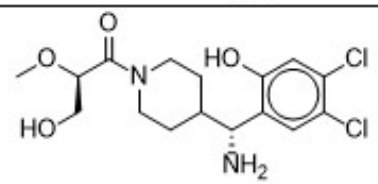
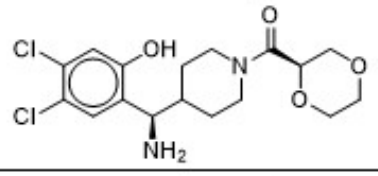
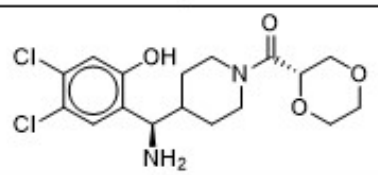
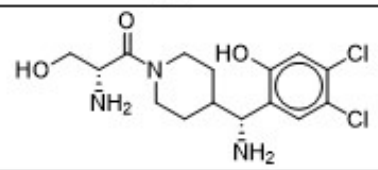
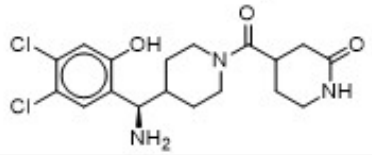
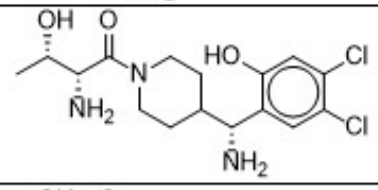
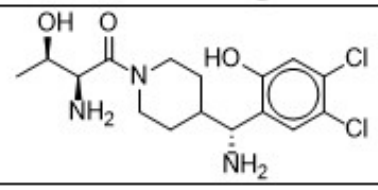

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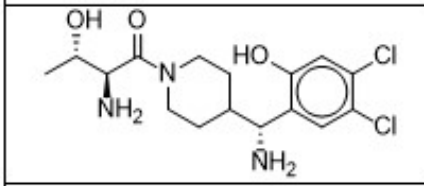
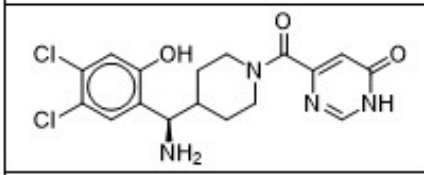
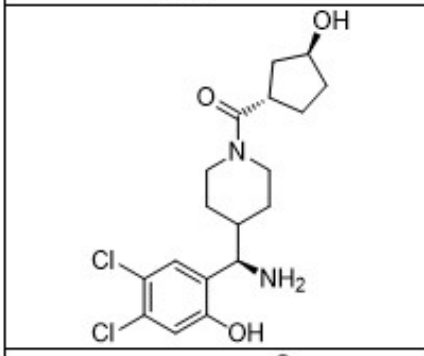
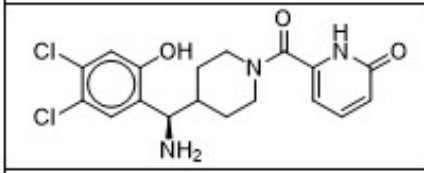
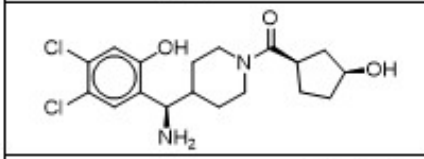
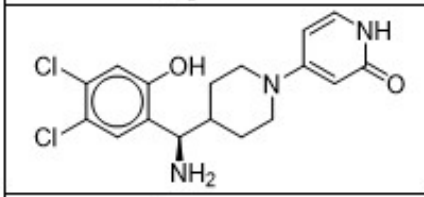
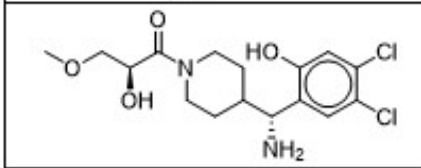
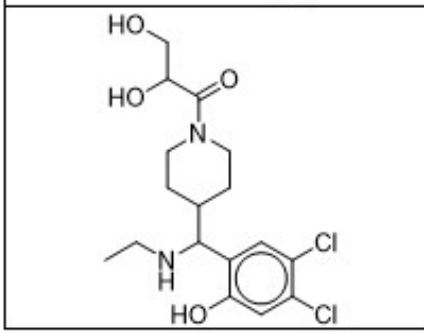

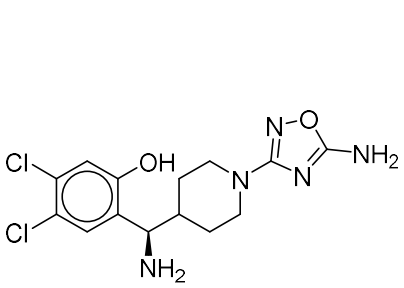

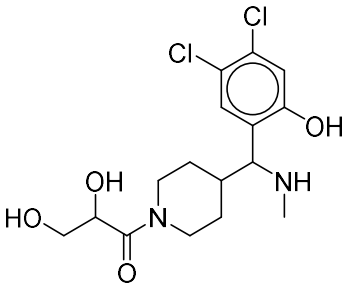

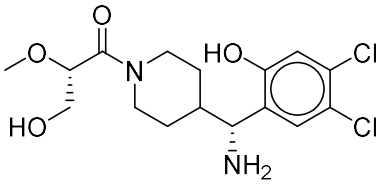

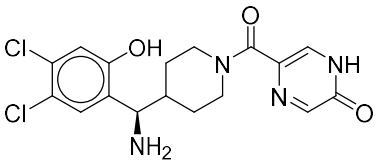

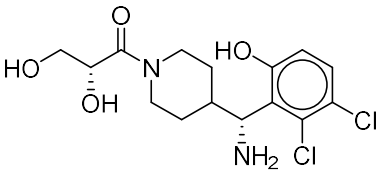

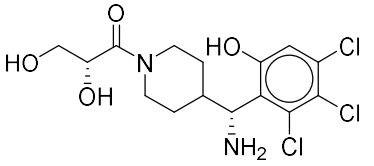

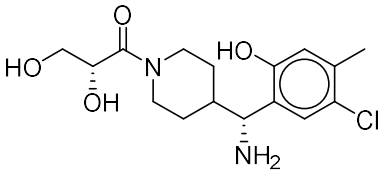

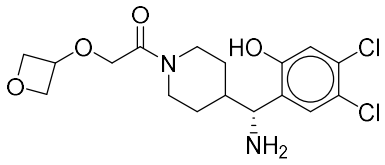

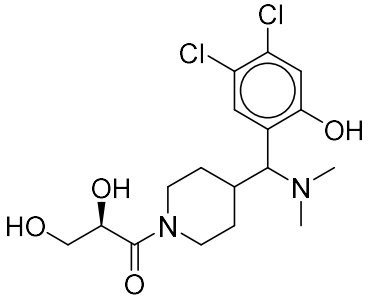

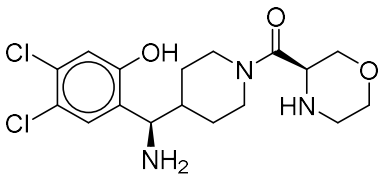

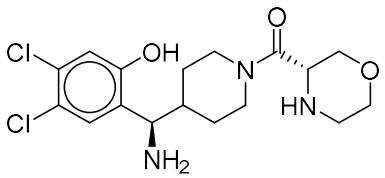

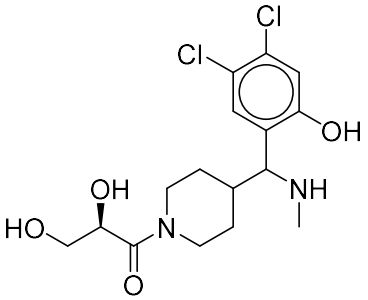

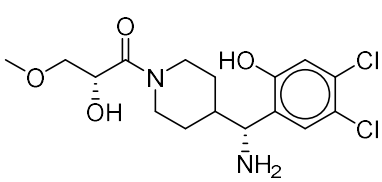

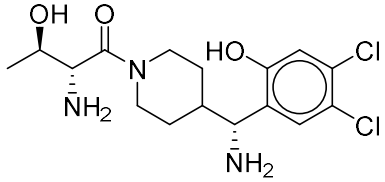

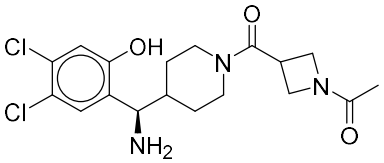

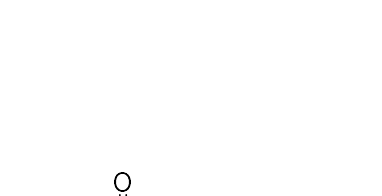

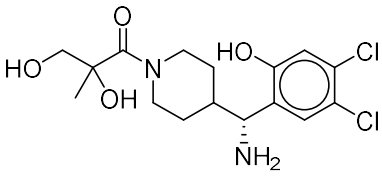

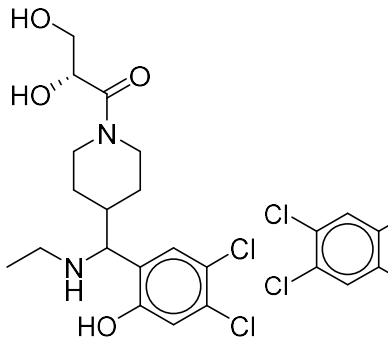

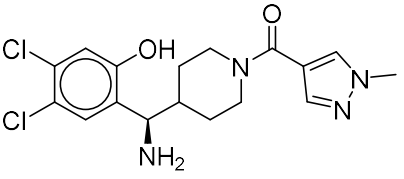

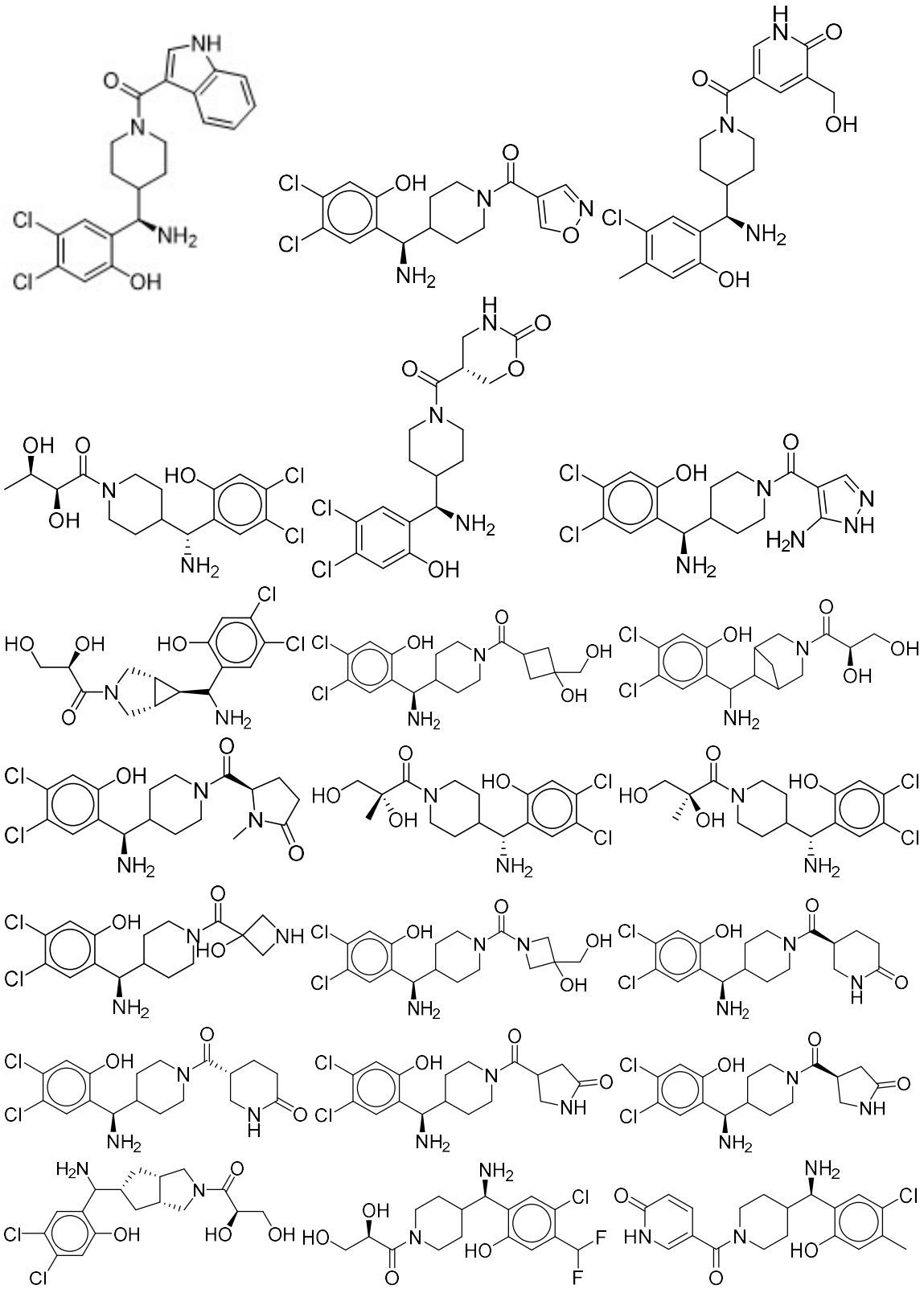

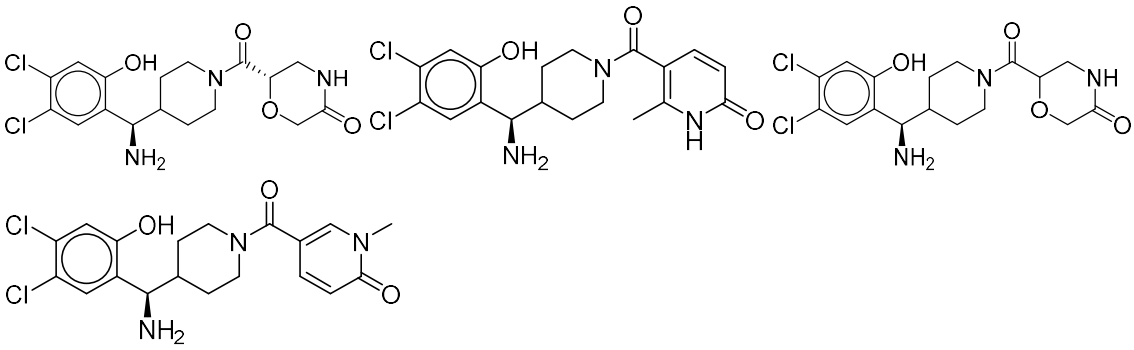

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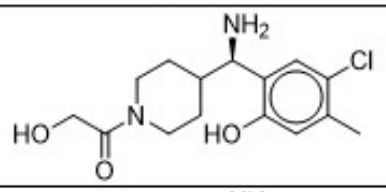
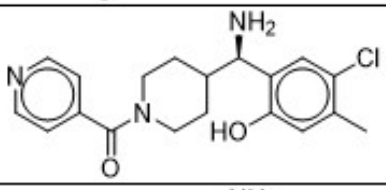
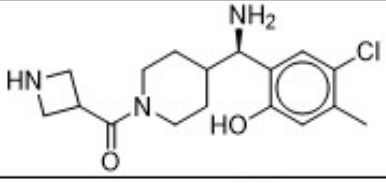
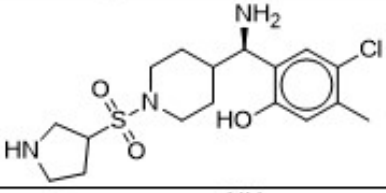
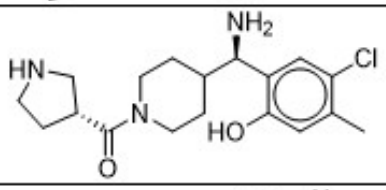
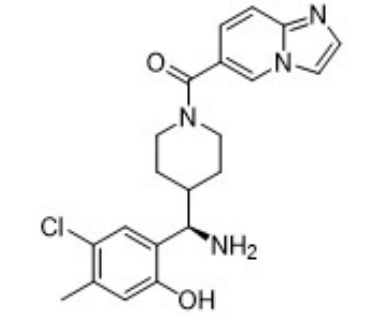
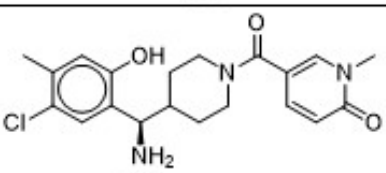
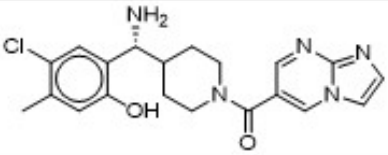
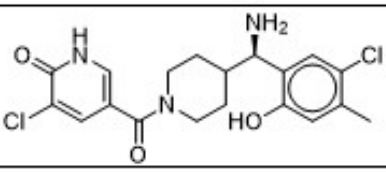

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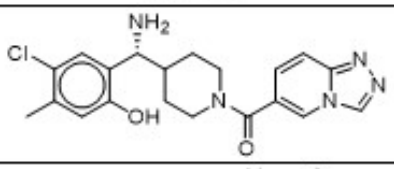
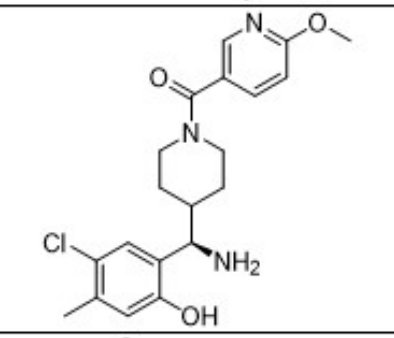
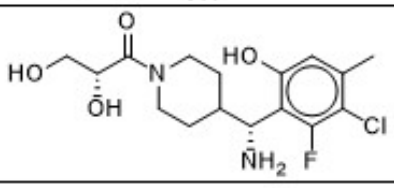
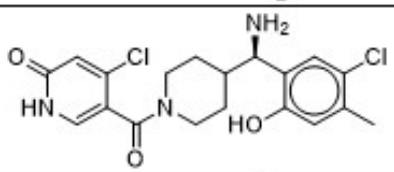
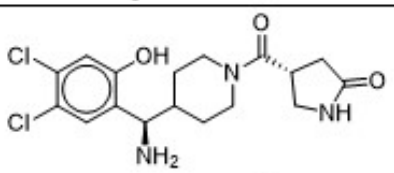
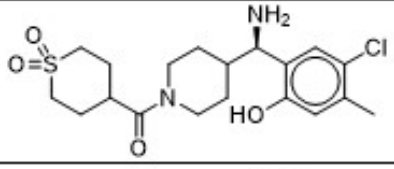
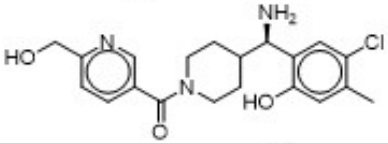
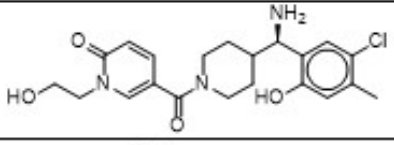
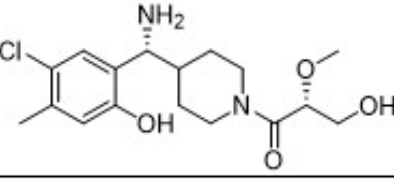

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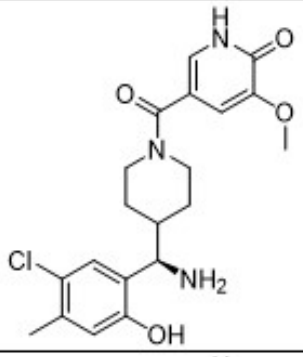
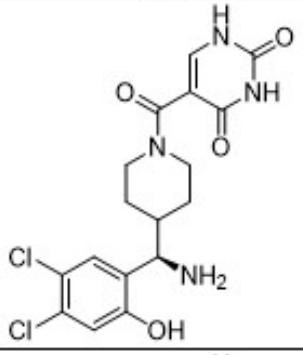
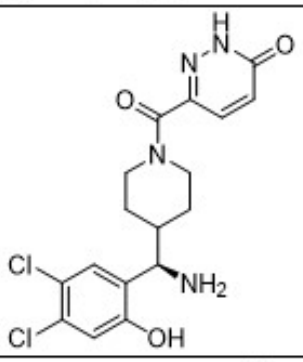
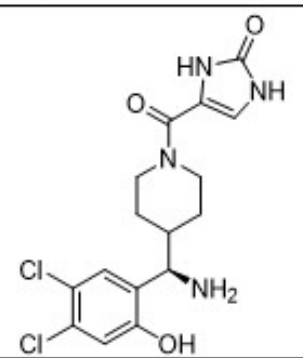

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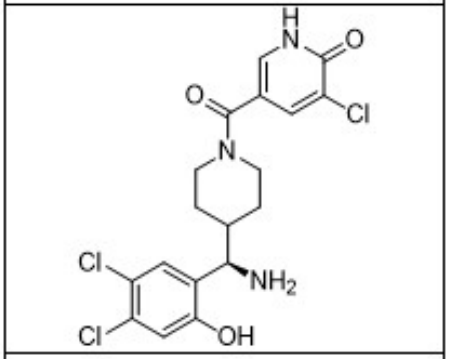
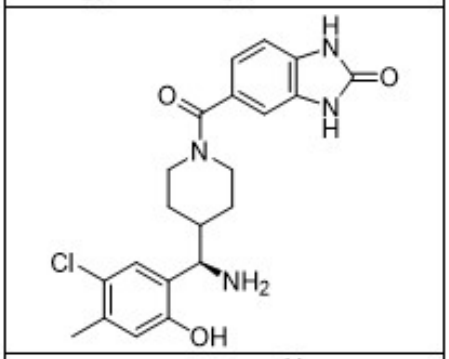
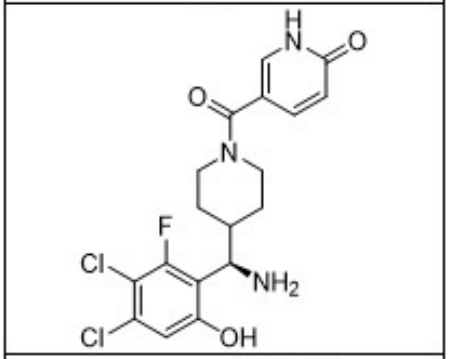
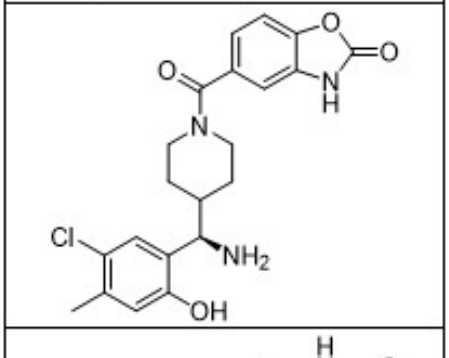
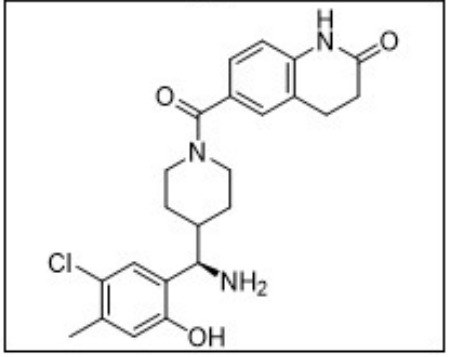

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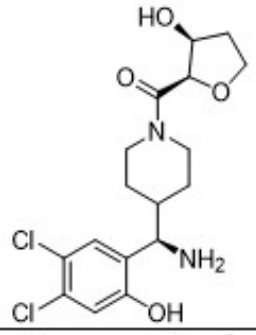
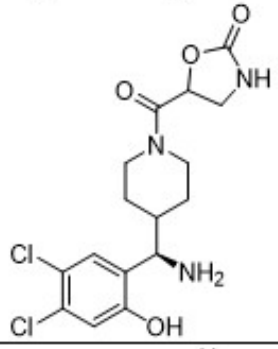
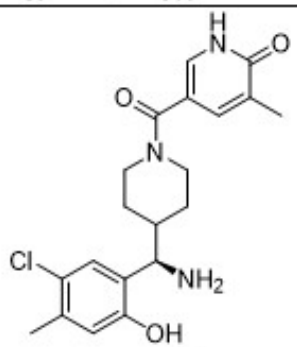
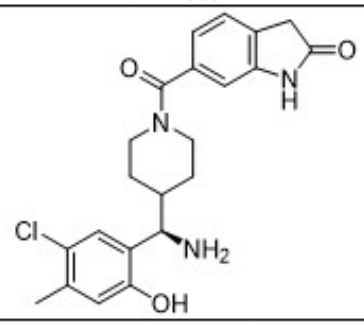
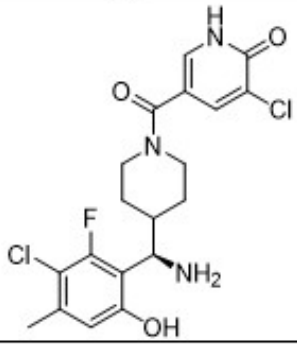

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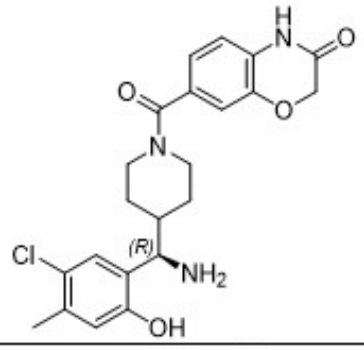
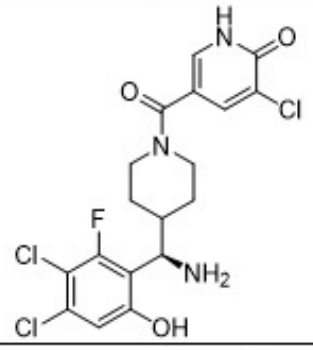
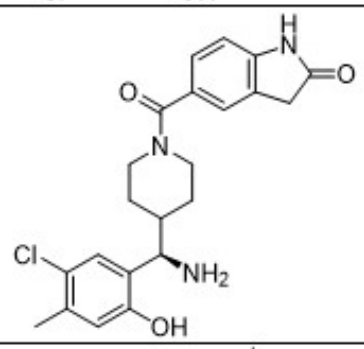
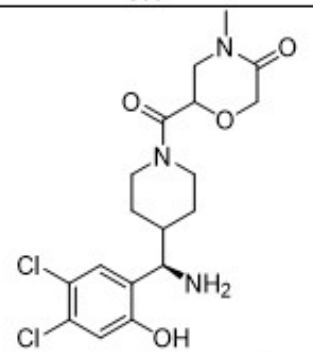
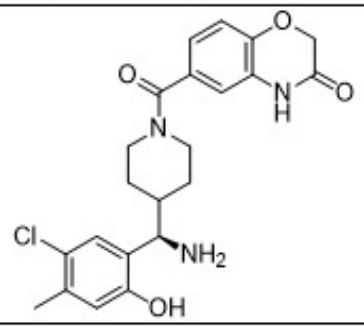

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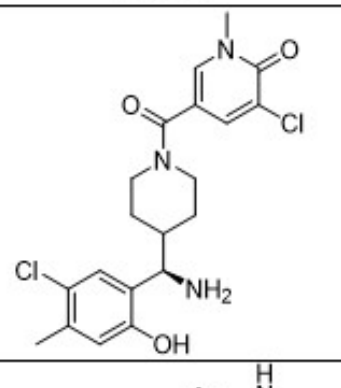
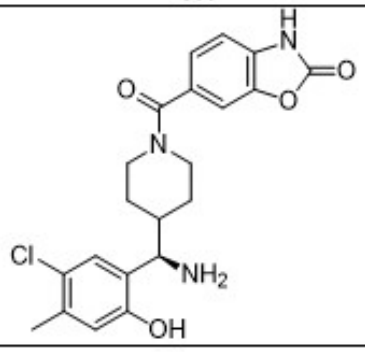
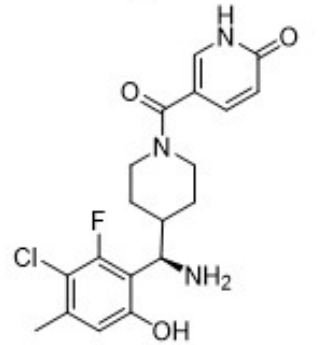
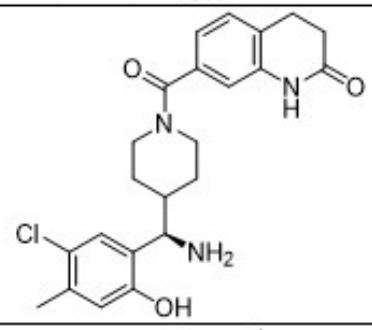
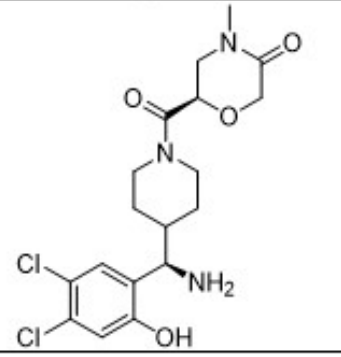

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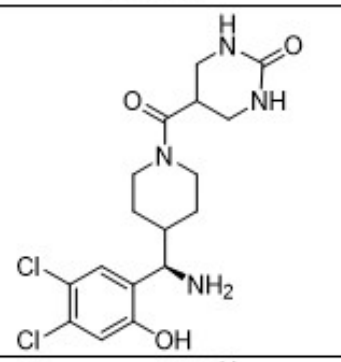
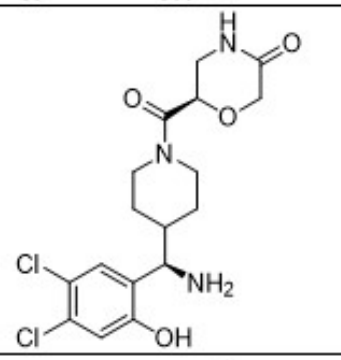
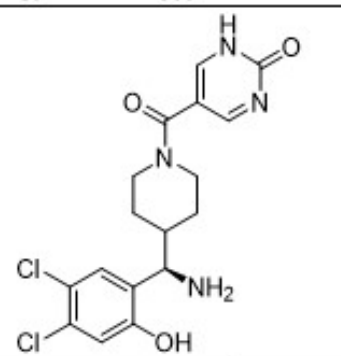
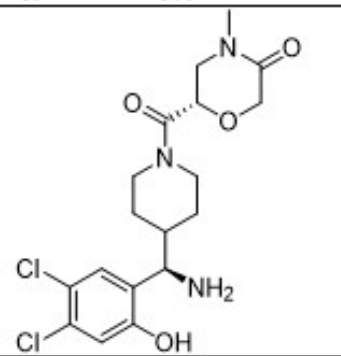

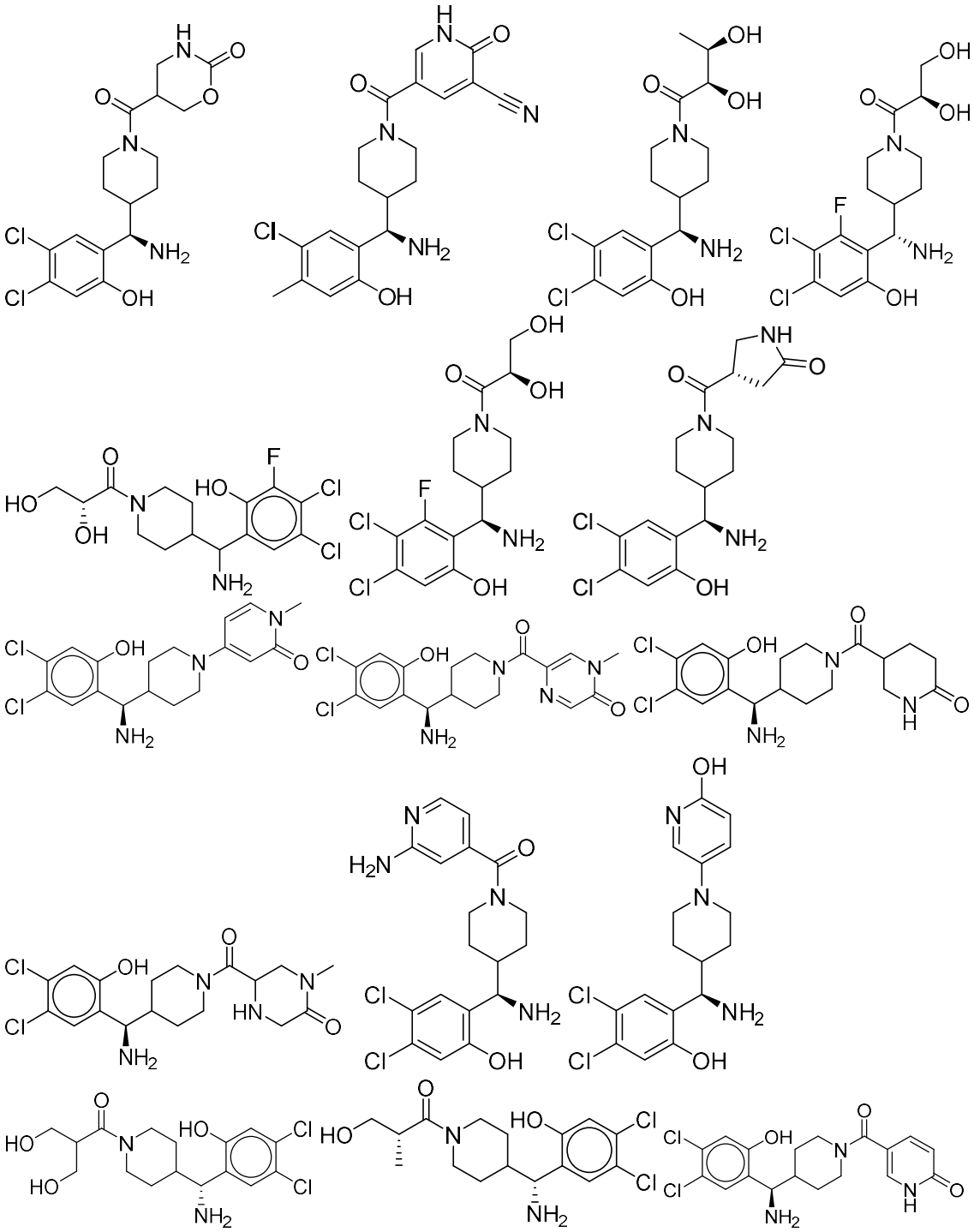

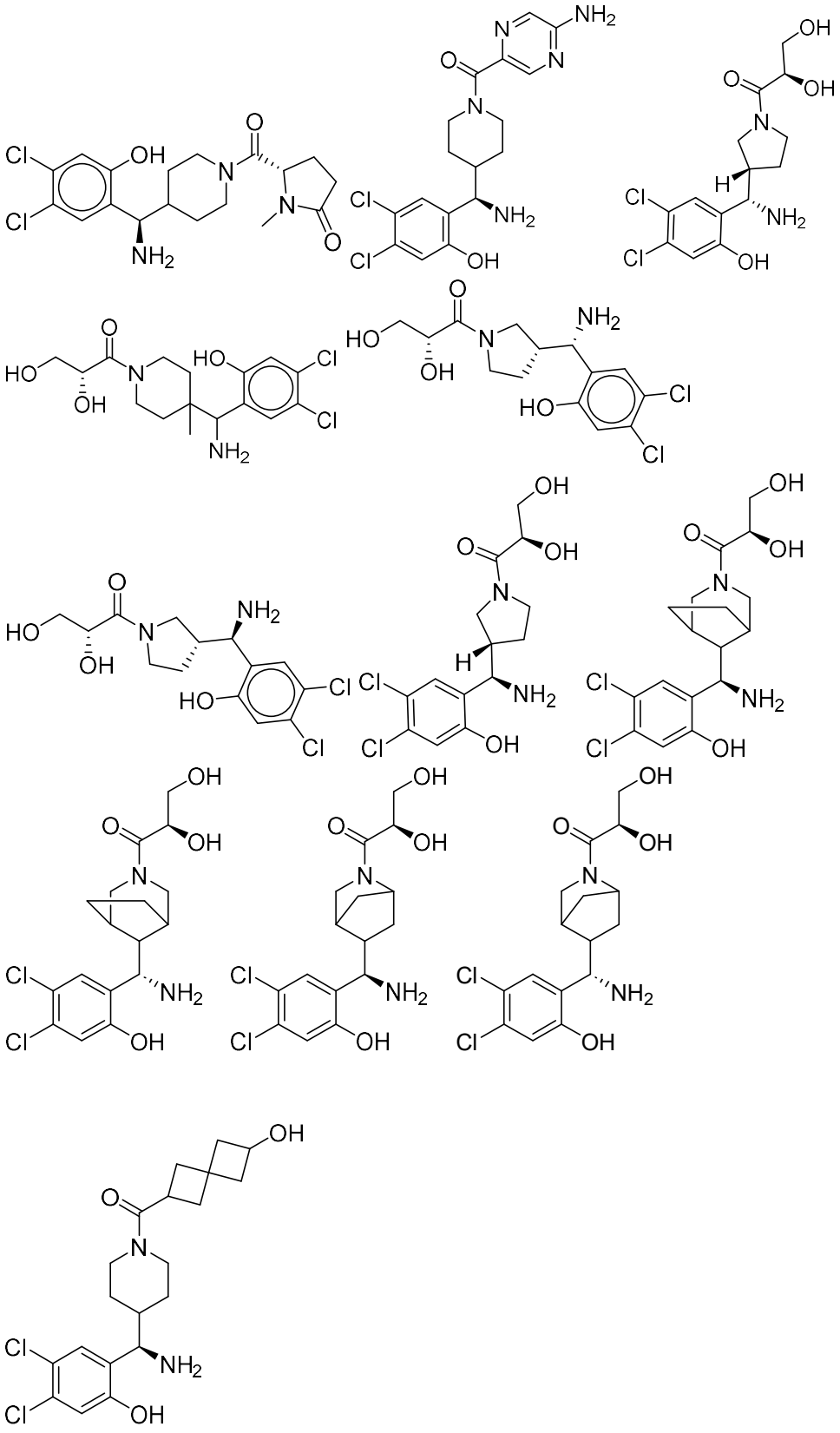

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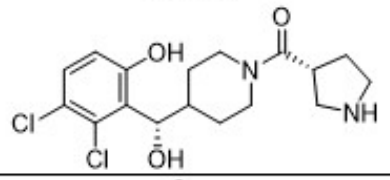
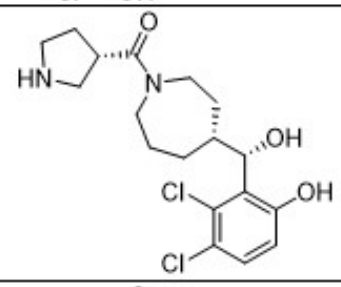
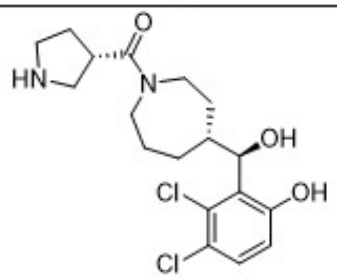
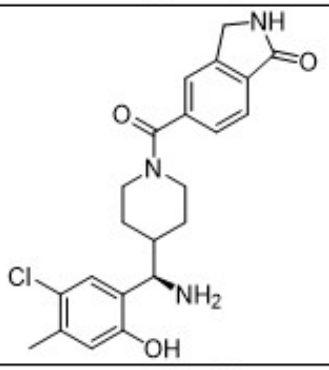
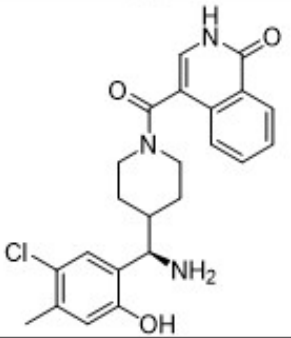

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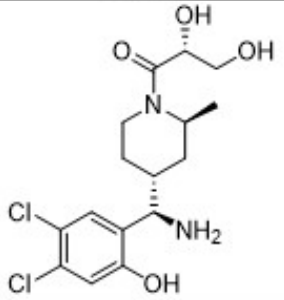
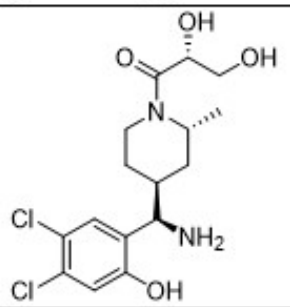
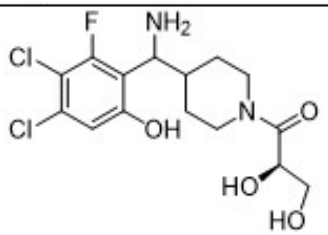
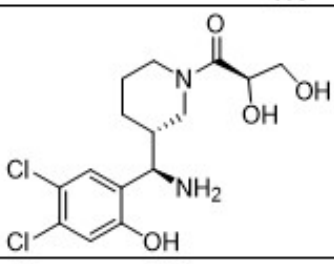
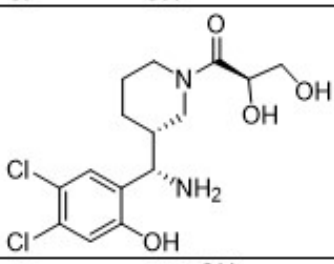
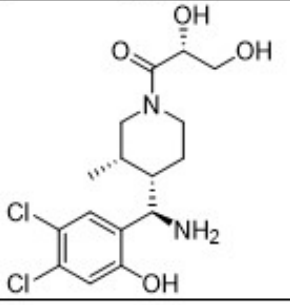

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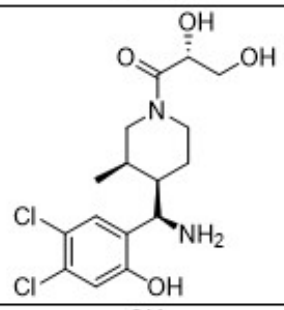	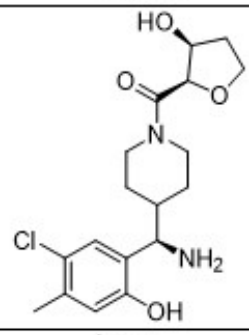
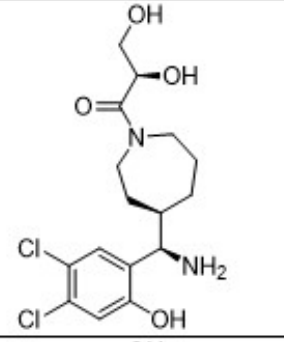	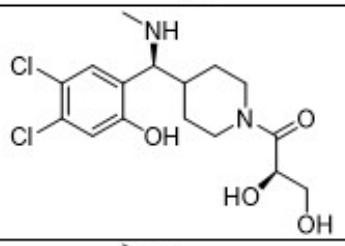
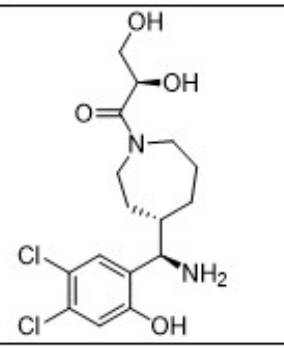	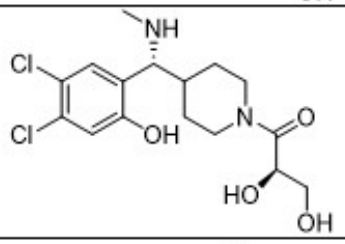
	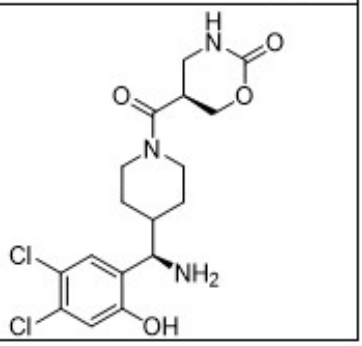

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22. A pharmaceutical composition comprising at least one compound according to any one of claims 1-21 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

23. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-21 for use as a medicament.

24. Use of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-21 in the manufacture of a medicament for treating a condition in a mammalian

species in need thereof, wherein the condition is selected from the group consisting of cancer, an immunological disorder, a Central Nerve System (CNS) disorder, an inflammatory disorder, a gastroenterological disorder, a metabolic disorder, a cardiovascular disorder, and a kidney disease;

optionally wherein the condition is:

(a) an immunological disorder that is transplant rejection or an autoimmune disease, wherein the autoimmune disease is optionally rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, or Type I diabetes mellitus; or

(b) a Central Nerve System (CNS) disorder that is Alzheimer's disease;

(c) an inflammatory disorder that is an inflammatory skin condition, arthritis, psoriasis, spondylitis, parodontitits, or an inflammatory neuropathy;

(d) an gastroenterological disorder that is an inflammatory bowel disease; or

(e) a metabolic disorder that is obesity or Type II diabetes mellitus; or

(f) a cardiovascular disorder that is an ischemic stroke; or

(g) a kidney disease that is chronic kidney disease, nephritis, or chronic renal failure; or

(h) selected from the group consisting of cancer, transplant rejection, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Type I diabetes mellitus, Alzheimer's disease, inflammatory skin condition, inflammatory neuropathy, psoriasis, spondylitis, parodontitis, Crohn's disease, ulcerative colitis, obesity, Type II diabetes mellitus, ischemic stroke, chronic kidney disease, nephritis, chronic renal failure, and a combination thereof;

and optionally wherein the mammalian species is human.